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THE

AMERICAN JOURNAL

OF THE MEDICAL SCIENCES

MAY, 1926

ORIGINAL ARTICLES.

THE ADVANCEMENT OF EPIDEMIOLOGY THROUGH EXPERIMENT.*

By Simon Flexner, M.D.

II. Experimental Results.

(From the Rockefeller Institute for Medical Research, New York)

In September, 1918, a spontaneous epidemic of mouse typhoid appeared in a breeding population of 2500 mice at the Rockefeller Institute and continued, with intervals of low death rate, for two and a half years during which time, through natural increase, the total numbers fluctuated between 1500 and 4000. The epidemic was followed closely, a mortality chart was kept, dead animals were autopsied systematically and occasional bacteriologic examinations were made. The epidemic finally ended, the cessation being hastened probably by systematic inoculation with killed cultures of the mouse-typhoid bacilli isolated from succumbing animals.[17] It was the timely occurrence of this epidemic which afforded the direct impulse to the experimental studies, still being pursued, the outcome of which will now be presented.[18] It is, however, proper to record that our minds were receptive, ready, as one might say, to take advantage of this chance offering to study epidemics thus directly in animals, as the result of experiences with recent epidemic diseases in man.[19]

When the decision was made to attempt the experimental repro-

* Part II of the Weir Mitchell Oration, delivered at the College of Physicians, Philadelphia, December 16, 1925.

duction of epidemics of mouse typhoid, Amoss and I were not aware that a similar undertaking was well under way in England. Topley, whose investigations have been so fruitful had already made a partial report in his Gulstonian Lectures which had just appeared in print.[20] Our plan differs somewhat in detail from the one Topley followed, for while Topley mingles infected and healthy mice introduced at intervals in large cages, Amoss and I set up a kind of mouse village in order to follow as closely as possible the spread of disease from cage to cage. In both instances the epidemics were started by feeding a small number of mice pathogenic cultures of a mouse-typhoid bacillus (enteriditis—paratyphoid group of bacilli). After a few days' interval or incubation a part of the fed mice developed and later succumbed to infection. To this source of disease healthy mice were exposed, either immediately, as in Topley's, or mediately, as in Amoss' and my experiments. We depended on the transfer of bacilli taking place through contamination of the hands of the attendant who fed the mice and cleaned the cages, very much as we suppose happens in spontaneous epidemics; it is interesting to note that no degree of mechanical or chemical disinfection sufficed to render the attendant's hands free of the bacilli.

In the half dozen years which have elapsed since the investigations have been under way there has been a good deal of parallelism between the experiments carried out by Topley, and Amoss, Webster, Pritchett and myself, and latterly by Neufeld and Lange, the actual results of which have been remarkably harmonious although the interpretations have not always coincided. There have also been differences in kind of experiment, according to the progress made in London or New York, and to the deductions separately based on the results obtained, as inevitably happens among experimenters and is conditioned by the particular imaginative outlook of one or another group of workers.[21] It is a pleasure to record that between the English and American investigators the best of feeling has always prevailed, and through correspondence and actual visits the progress of events has been closely followed, and thus far without the slightest conflict and with common advantage all around.

It became immediately evident that it was possible to start continuing epidemics of typhoid among a healthy mouse village population, from which it was concluded that a wide, if not uniform, distribution of the bacilli was quickly effected by the attendant, leading to infection and death of some but not all the mice exposed. At the outset the number and distribution of deaths in the separate cages simulate the sporadic happenings noted often to precede the real epidemic outbreaks. This preëpidemic variety of the disease was later, as will appear, converted into a true epidemic prevalence, in which groups of mice sickened and died

according to an order, suggesting, if only roughly at first, the periods or following waves of the spontaneous mouse epidemics, or epidemics as observed in man. The explanation of these events, observed by Topley in his single cage experiments and by us in the mouse village, was not at first wholly perceived. Topley ascribed them chiefly to rise and fall of bacillary infectivity, Amoss and I to fluctuations of virulence plus dosage of the bacilli. Later the discrepancies could be accounted for by Webster, who determined the interaction of three quite constant factors, namely, level of virulence of the bacilli, quality of resistance of the host or exposed mice, and quantity of bacilli ingested or dosage.[22]

To enable you to follow the succession closely, let me state that in Topley's experiments once infection was started fresh increments of healthy mice were placed in the cage at intervals. In Amoss' experiments once a kind of equilibrium or stationary period of disease arose in the village, cages containing fresh, healthy mice were brought into contiguity with the previously exposed animals. In order to be brief, I will give you the bare results of a long series of observations of successive waves of mouse typhoid followed by recessions, thus induced, in which not only the new animals but the old or already exposed ones also were affected.

In three separate experimental attempts to induce outbreaks of mouse typhoid resembling the epidemic spread witnessed in breeding stocks and spoken of as arising spontaneously, the type of disease induced was first that of the sporadic prevalence, as shown by the number of mice dying and the number of cages attacked. Once, however, this state of sporadic disease is started in a mouse population, all that appears necessary in order to convert the occasional deaths with low cage-attack rate into frequent deaths with high cage-attack rate, is to bring into contiguous relation with the infected population increments of not previously exposed healthy mice.[23]

The sporadic prevalence is quickly over. The new mice having been introduced, the succeeding events proceed in an orderly fashion. After an interval of about five days the latter, or new mice, begin to die, the number of deaths and the proportion of cages attacked rising day by day. During the first period in which the new mice fall victims to the disease the old mice do not show an increased death rate. *But from the tenth to the twentieth day after the addition of the new mice, and hence the fifth to the fifteenth day following their deaths, the old mice are drawn into the wave of fatality, with the result that ultimately they suffer a mortality equal to or even greater than the new ones.*

The epidemics thus inaugurated, as indicated by the deaths, usually diminish or even disappear before all, sometimes after only a small part of the exposed mice have been destroyed. A tendency shown by all the experiments is for a state of equilibrium

between the surviving mice and the infecting bacillus to be effected, this state continuing until fresh infectible material is provided, when there arise undulations or epidemic waves of deaths remarably uniform in respect to the successive replacements of fresh mice. The undulations cease gradually, the late fatalities resulting not from delayed infection so much as from protracted illness and long survival. Bacillus carriers arise in the course of the epidemics and show, through possession of agglutinins, the existence of a partially immune state. It is through these carriers that the disease is propagated, in spite of which, as the events prove, the partially immune individuals are not themselves adequately safeguarded, since as we have seen, the older mice which have weathered one or more epidemic storms ultimately sicken and succumb. Here obviously another factor operates, and this all-important one in overcoming natural and acquired resistance is the factor of quantity or dosage of the bacilli.[24]

Topley, as already pointed out, and his predecessor, Danysz, considered fluctuation in virulence as the factor which chiefly determined the waves of epidemic prevalence of mouse typhoid, and Flexner and Amoss regarded the virulence plus dosage as the deciding events. But it was the precise studies of Webster and Pritchett, on the constitution of the bacilli on the one hand and the reaction of the host on the other, which have yielded the constants with which to measure the actual happenings observed.[25]

We are, as one might say, in sore need of the simplification of the phenomena of the epidemic, which happily an accurate study of the living materials and other effective agencies seem capable of supplying. We need to measure not only bacilli and host, but such other factors as diet and season, if we wish to bring animal and human epidemic occurrences into harmonic relationship. Undoubtedly, certain of these extrinsic influences have been included in the term "telluric," as used by the older epidemiologists. Fortunately we may subject certain of the "influences" to experimental verification in order to introduce precision into our calculations, in opposition to such vague notions as "epidemic constitution." It would seem not inappropriate to introduce at this point of our discourse the significant words with which the young army surgeon, Helmholtz, as he was then, closes the introduction to the treatise giving to the world the mathematic physical demonstration of the conservation of energy, based in part, as you may recall, on physiologic studies carried out on voluntary muscle. He says: "Theoretical natural science, therefore, if she does not rest contented with half views of things, must bring her notions into harmony with the expressed requirements as to the nature of simple forces, and with the consequences which flow from them. Her vocation will be ended as soon as the reduction of natural phenomena to simple forces is complete, and the proof given that this is the only reduction of which the phenomena are capable."

With this ultimate purpose in mind we may now proceed to an analysis of the phenomena of mouse typhoid as experimentally induced in relation to such factors as constitution of bacilli, response of host and influence of dosage, diet and season, as determined by the precise studies of Webster and Pritchett upon homogeneous stocks of mice.

Bacilli were administered *per os* by means of a simple mechanical device, which delivered a fixed quantity, approximately 4,000,000 organisms, into the stomach. Five strains of enteriditis paratyphoid bacilli were tested on about 1400 mice. Stools and blood were studied by culture, and blood was tested for agglutinins. Three groups of mice were distinguished. In the first group the bacilli disappear at once or after a brief period from the stools, and the blood is persistently negative for bacilli and agglutinins; the 20 to 30 per cent of mice composing this group continue well during the eight-week period of observation. In the second group the bacilli are passed for an irregular period; small numbers invade the blood and agglutinins are present and strong three weeks after the inoculation. The 5 to 10 per cent of the mice composing this group sicken but recover. The members of the third group pass large numbers of bacilli, many are cultured from the blood during life, and the 70 to 80 per cent of mice composing it sicken after five days' incubation and sooner or later die. The five bacillary strains differed among themselves in degree of virulence, but each one remained constant in its pathogenic action upon mice and was unaffected by animal passages. It could be shown, therefore, that the epidemic outbreak of greater or less severity of mouse typhoid is determined in large measure by inherent degree of bacillary virulence. An originally highly pathogenic strain is more destructive than an originally less active one, and antigenic identity is no measure of infective equivalence. In other words, the occurrence of two strains of the bacilli pathogenetically different and antigenically identical does not indicate transmutation of one into the other. When suitable tests are carried out by intraperitoneal inoculation the same general rules regarding virulence fixity of strains are found to apply.[26]

In order to determine the limits of the host response the effect of varying dosage has first to be ascertained. When fixed quantities of cultures of given strains of mouse-typhoid bacilli are introduced into the stomach of mice of selected weight, and of the same lots as regards parentage and food, consistent results, as shown by the percentages of those surviving and succumbing, are obtainable. When massive doses of the bacilli are given the deaths fluctuate between 70 and 80 per cent; when critical doses are given the percentages vary from 40 to 50. When infection is permitted to take place by contact of inoculated with uninoculated mice the end result is determined by the relative numbers of each kind in the combina-

tion. Thus when 5 inoculated mice are placed with 1 uninoculated animal the percentage mortality of the latter corresponds with that of the purposely inoculated, while when the ratio of inoculated to uninoculated is 1 to 1 the effect of the contact is very small.

These findings bring out two important points, namely, that the the susceptibility of a mouse population to mouse-typhoid infection is a relative or graded property; and that the dosage, as determined by the quantitative and spatial distribution of the bacilli, is a definite factor or constant, as shown by the mortality curve. A significant corollary to the findings is that irrespective of reasonable dosage and of strain of bacilli, from 20 to 30 per cent of mice ordinarily resist infection.

The statement just made regarding resistance indicates that using sufficient numbers of mice, the quality or degree of host susceptibility or resistance, according to the angle from which the results are viewed, may be found also to be a constant. Thus 540 mice of the same age and weight, bred at the Rockefeller Institute, were given *per os* a standard dose of culture of a mouse-typhoid bacillus. The mortality curves of the several tests were remarkably uniform. There were, it is true, minor variations which later, and as will appear, could be correlated with seasonal changes. The figures yielded by this large number of mice were employed to construct a so-called *standard control curve*, with which other curves could be profitably compared. For example, it was found that when mice were drawn from other sources and inoculated in an identical manner the curve differed from the standard one. Thus, mice procured from a Pennsylvania source yielded a curve lower than the standard, and mice from a New Jersey source, a curve exactly agreeing with the standard.[27]

This constancy of response among groups or stocks of mice to given strains and doses of the bacilli, suggested to Webster that after all the determining qualities residing within the animals might well be not of specific so much as of nonspecific nature, and something which comes into play, no matter what the nature of the poisonous agency may have been. With this idea in mind, he administered bichlorid of mercury also by stomach tube to groups of mice. It happened that with a dosage of 0.0033 gm. the mortality curve exactly parallels the standard curve. With larger and smaller doses of the drug curves are obtained reproducing those yielded by culture strains of higher and lower degrees of virulence.[27]

Up to this time the host material consisted of mice of common stocks, but not of pure line origin. That heredity may affect the degree of susceptibility could be assumed. Fortunately, material was available to test this point directly, as was done by Pritchett. Two sets of experiments, extending over two years and involving five separate strains of mice and 5000 individuals, were made. The strains consisted of three pure-line lots yielded by brother-sister

matings and two homogeneous lots obtained by close inbreeding. During the first year 500 and during the second year from 300 to 600 mice of each strain were inoculated *per os* and closely followed. The result of this laborious study leaves no doubt that definite differences in susceptibility to typhoid exist among mouse stocks and that hereditary factors play an essential part in determining variations.[28]

Having now ascertained that the quality of the host plays a leading or decisive part in mouse-typhoid infection, it would seem to follow that the mice resisting bacterial infection should be the ones responding least to mercury bichlorid poisoning, as indeed was found by Webster to be the case. Moreover, he also found that when mice surviving ordinary lethal doses of mouse-typhoid bacilli are inbred for several generations, the offspring become progressively more resistant both to the bacilli and to mercury bichlorid; conversely, the offspring of females belonging to families of high susceptibility show the opposite tendency, and are less resistant to bacilli and chemicals than the corresponding unselected mouse material.[29]

With these data before us, we may turn for a brief consideration of certain of Topley's findings for which he gave no adequate explanation. It will be recalled that he assembled mice in large cages to which fresh animals were added at intervals. He found that when the additions were made in the period of decline of the epidemic the fresh mice were more likely to survive than when they were added at the ascent of the wave; also when the additions were made daily the deaths did not occur regularly, but came in waves nevertheless. Topley ascribed these happenings mainly to supposed fluctuation in virulence of the bacilli. We now know, thanks to Webster's accurate studies, that the bacilli do not so fluctuate, and we have also learned that host susceptibility and dosage of the bacilli largely affect infection and death. The probability, therefore, is that the wavelike movements, observed originally by Danysz and later by Topley and ourselves, in the course of mouse-typhoid epidemics are determined by the quantitative distribution or concentration of the bacilli acting on mouse populations previously unexposed or exposed. In all instances first the former and next the latter are affected, according to the measure of original susceptibility and subsequent available quantity of bacilli. That this is the usual series of events was shown by Pritchett in a conclusive way. She devised means of estimating at two or three days' intervals the number of mouse-typhoid bacilli in a cage containing an infected population, to which daily additions of 2 healthy mice were made. The tests carried over a six-month period showed definitely that the mortality rate rose regularly six to eight days after a large increase took place in the number of bacilli in the cage.[30]

Dosage of bacilli, therefore, in mouse typhoid—just as concentration in certain infectious diseases in man—is found to be a significant factor in initiating epidemics. It is well known that in order to diminish greatly, or even to abolish altogether malaria and yellow fever, we need not eliminate all the mosquito vectors; what is aimed at is to reduce the number to an established effective index, when the diseases disappear. When certain bacterial infections rage, streptococcus sore throat, for example, the number of carriers of hemolytic streptococci is large; as the malady abates, the number of carriers shrinks, and so with epidemic meningitis and other diseases. It is desirable that the fact be generally appreciated that in quantity of bacteria we have something which can break through the resistance barrier, be it natural or acquired. The persons vaccinated against smallpox or against typhoid fever, adequately protected under ordinary conditions of incidence of those diseases, may still be open to attack when the diseases become rampantly prevalent. The protective immunity mechanism is a measurable quantity, and may be superseded. When the quantity or dosage, so to speak, of the microbic assailant is large, and the grade of virulence high, even the extraordinary defenses of the body may prove insufficient.

We have now reviewed the inherent factors, microbe and host, as we may call them, as they react on each other, in the course of those happenings through which epidemics are generated. It will, I think, be admitted that the knowledge gained by the experimental method of study of the phenomena displayed by mouse typhoid is enlightening. In how far the data secured can be applied to other epidemic diseases and to hosts other than mice, has still to be determined. We know already, thanks largely to Webster's investigation of Bacterium lepisepticum infection in rabbits, that they are applicable to them.[31] But we have still to consider certain external or environmental influences which affect the course of mouse typhoid and doubtless of other diseases as well. I shall deal, at this time, especially with the influence of food and of season on the course of mouse-typhoid infection.

That food should play a part in altering the course of an epidemic disease might perhaps be inferred from the profound effects produced by dietary deficiencies as expressed in beriberi, rickets, scurvy and possibly in pellagra. We shall deal, however, in this instance with no such extreme departures from the ordinary in diet. Indeed, it has been found—and just this is the surprising thing—that a diet to all intents and purposes adequate and favorable may nevertheless affect a stock of mice injuriously in comparison with another diet more ideally, as it seems, adjusted to their requirements.

Webster and Pritchett's experiments on food effects were simple in design. Two sets of mice were employed. One set was reared

on the regular Rockefeller Institute ration in use for many years, and consisting of a daily feeding of baker's bread soaked in grade B pasteurized milk and warmed to 60° to 70° C., and supplemented by two weekly feedings of an oatmeal-buckwheat mixture and one weekly feeding of dog biscuit. The animals thrive and multiply on this diet. The diet with which this was compared was McCollum's normal one for rats and mice, consisting of wheat, 67.5 per cent; casein, 15 per cent; milk powder, 10 per cent; sodium chlorid, 1 per cent; calcium carbonate, 1.5 per cent; butter fat, 5 per cent. The mothers and the offspring, the latter being taken for experiment, were fed the McCollum mixture. Equal groups of mice fed on the two diets were given by stomach tube either about 4,000,000 mouse-typhoid bacilli or bichlorid of mercury. A very few of the mice were tested by intraperitoneal injection of 1 minimum lethal dose of botulinus toxin. The mice fed on the McCollum diet proved to be less susceptible to all three injurious agents. As the effect of the diet is directed against chemical as well as biologic poisons and in equal degree, we are justified in speaking of the defensive mechanism involved as nonspecific. This fact leads to the important conclusion that the factor which we so commonly invoke under the names of susceptibility or resistance is an innate quality of the host, brought into play under stress and strain of injury of widely various nature.[32]

Seasonal variations of disease are, of course, very well known. Even when we exclude those diseases which depend upon insect vectors whose prevalence is determined by season, we still meet with examples which display strong seasonal fluctuations. The influence of season was tested on 5900 mice by Pritchett in two sets of experiments covering the twenty-four months' period from 1923 to 1925. A given number of mice, consisting of three pure-line and two homogeneous strains, was inoculated by stomach tube every month with about 5,000,000 mouse-typhoid bacilli of fixed virulence. Each test was run for eight weeks, the deaths being recorded daily and routine bacteriologic examinations being carried out. Not only were seasonal variations displayed, but they were remarkably uniform over the two twelve months' periods; yet certain, if slight exceptions arose. As the mouse material was by heredity of heterogeneous nature, certain differences in response to infection resulted from that circumstance. And yet it may be stated that the course of events was uniformly such that the mortality curves tended to arrange themselves into three series, namely, curves indicating: (*a*) High spring mortality; (*b*) low summer mortality; (*c*) intermediate fall and winter mortality. Expressed in terms of deaths, we may say that the spring rate is high, the summer rate low and the fall and winter rate, while falling between the two, may in the early fall rise sharply and even approximate the spring level. Since, however, the seasons, year by year, are

only roughly comparable and vary in temperature, sunlight and other conditions week by week or month by month, a certain amount of fluctuation in the curves is to be expected, provided that it is affected, as it appears to be, by meteorologic occurrences.[33]

It would be desirable, in view of recent discoveries of the profound effect of light in protecting the animal organism from rickets through its influence on the calcium metabolism, to study the part which it may play in epidemics. Indeed, the recent precise studies of Brown and Pearce on the effects of sunlight, especially on the normal as well as on the pathologic organism, already point to important correlations. They have secured data from 400 normal rabbits, observed month by month over a period of three years, and a like number of rabbits inoculated with a malignant tumor and with syphilis, similarly studied. They have found first that, contrary to current belief, no fixed relation of size and weight attaches to the individual organs, but that the relationships are constantly changing in a more or less rhythmical manner. Hence what might be regarded as normal at one time would be regarded as abnormal at another time. The weights of the heart, liver, kidneys, and even the brain in proportion to body weight, fluctuate in the course of a year as much as 20 to 40 per cent; while the endocrine organs, lymph nodes and spleen show variations of 50 to 100 per cent. Constant readjustments of the relative balance among the various organs of the body takes place, and this system of changes follows a regular course which may be correlated with the seasonal changes of the year. So far the meterologic condition which occupies the place of most importance is sunlight. Just as the organs increase and diminish in relative size, so it appears does the severity of the tumor and the manifestations of syphilis in the rabbit rise and fall according to the organic changes. From this it may be inferred that the seasonal variations affect functional activity in that they coincide with or induce alterations of the state of the animal body with which pathologic effects are related.[34]

We have now arrived at a natural halting place in this discourse, from which to view the ground that has been covered. We may, I believe, discern a certain order and sequence of events in determining epidemic occurrences in at least one infectious disease in animals. Not only may the origin of the mouse-typhoid epidemic be accounted for by the presence of the offending bacillus, but the course pursued is, as it were, predictable on the basis of the constitution of microbe and host, as affected by such modifying causes as dosage and particular environmental conditions. The preponderant rôle of dosage and fresh infectible host material is clearly indicated in prolonging the epidemic and explaining the periodic wavelike movements. That the spontaneous epidemics of mice are prolonged in an identical manner by new births and by the spatial and quantitative distribution of bacilli may be assumed as quite

certain. Application of these findings to the study of epidemics of human diseases in which more precise observation shall take the place of actual experiment is the possibility clearly indicated. Perhaps in this manner will the next forward step be taken leading to the solving of riddles in epidemiology as related to man.

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THE RELATIONSHIP OF SULPHEMOGLOBINEMIA TO HEPATIC DEFICIENCY, WITH REPORT ON A CASE.

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Sulphemoglobinemia is a rare disease; the present case is the twenty-fourth or twenty-fifth on record. It shows that the boundaries between the autotoxic parhemoglobinemias are not rigid and also illustrates one danger of prolonged ingestion of the coal-tar analgesics. The case is therefore of interest and it is hoped that the suggested relationship to hepatic deficiency will add to a better understanding of the condition.

Case Report.—The patient, Miss H., aged thirty-one years, was admitted to the Bristol Royal Infirmary in January, 1924. She

stated that for the last seven years she has had attacks of abdominal pain associated with cyanosis and vomiting also that she loses consciousness during the attacks, and her urine is passed with difficulty and is dark in color.

She appears well nourished, her color is leaden, but no clubbing of the fingers or edema is present. Physical examination is negative except for some tenderness of the loins and over the symphysis pubis. During an attack shortly after admission the color became more deep, she vomited four times, she perspired profusely, complained of substernal pain and her pulse became more rapid. There was no loss of consciousness and the urine showed no alteration of color.

She had several similar attacks while in the hospital; each time there was the same deepening of the cyanosis but the cyanosis persisted in the intervals and was of about half of the intensity of that during the attacks.

After three weeks in the hospital she developed pyelitis, due to Bacillus coli and a streptococcus; this was treated with mercurochrome and subsided rapidly. Nine weeks later she complained of severe abdominal pain, she vomited several times and showed some distention. A laparotomy was performed but nothing beyond some adhesions was found; recovery was uneventful.

She received calomel for constipation, slight in degree; a vaccine, made from the streptococci in an apical dental abscess, was given and she was put on a high carbohydrate diet, at my suggestion. Her recovery was slow but steady and after four months her color was pinkish constantly. About this time she developed an erratic pyrexia which ceased when her method of producing it was discovered. A little later she developed attacks of transient cyanosis again, but during the intervals her color was normal. During one of these attacks I found the spectrum of methemoglobin in the blood and suggested that her urine should be examined for acetanilid and similar drugs; this was done by Mr. A. Taylor, M.P.S., who found salicylates and a trace of acetanilid. A search among her belongings revealed many packets of headache powders containing these substances. When the supply failed she had no more cyanosis and she was shortly afterward discharged in apparent good health.

Pathologic Investigations. On admission her blood showed a band in the red portion of the spectrum which was not removed by ammonium sulphid; artificially produced sulphemoglobin showed an identical spectrum. The spectrum band was deeper during the cyanotic attacks. It is regretted that Hurtley's[1] and van den Bergh's[2] tests were not made; these were deferred, through pressure of work, and when time was available the blood was normal. However, the tests actually made are very reliable. As the cyanosis lessened, the band in the spectrum disappeared. Later, when the cyanotic attacks were transient the spectrum of methemoglobin was found,

as was noted. It should be observed that the abnormal pigment was in the red blood corpuscles only, the serum and plasma did not show the spectrum.

Test meals showed no delay in the passage of food through the alimentary tract. The urine showed no abnormality on admission; later pyelitis developed, such pyelitis has been noted in several of the cases recorded. There was a decided oliguria; Violle's test gave a total of 448 cm. instead of the normal 830 cm.; a similar oliguria is noted in Long and Spriggs case.[3] The feces showed no abnormality. Sulphid-forming organisms were not present in any excess; the quantitative test proposed by Wood Clarke[1] was not made, as rough quantitative tests were normal. The saliva, urine and blood serum were tested many times for nitrites, using the Griess and Griess-Illosvay methods; the results were consistently negative except that on one occasion there was a faint doubtful positive reaction to the Griess test in saliva. As Vogel[4] showed that the saliva of normal persons sometimes contains nitrites, this finding is of little importance.

The blood showed a mild degree of anemia of secondary type; a similar degree is noted in most of the recorded cases. The leukocytes varied about 10,000 per c.mm. The Arneth index was 240 and 260 on two occasions. The fragility test of the red blood corpuscles gave incomplete hemolysis at 0.4 per cent and complete hemolysis at 0.32 per cent sodium chlorid with Sandford and Griffiths technique. Blood urea varied about 36 mg. per cent. The van den Bergh test gave a slightly increased amount of indirect bilirubin. Blood culture was negative.

The presence of reducing substances in the blood was frequently sought, but no evidence of their presence could be found. Oxyhemoglobin was not reduced, and sulphemoglobin was not formed from hemoglobin on incubation with the serum of the patient. The following test shows that the serum and corpuscles of the patient had no more affinity for sulphids than had normal controls:

Serum of patient and controls were separated from the red blood corpuscles and the latter were well washed. A freshly prepared saturated solution of hydrogen sulphid in normal saline solution was made. As a reducing catalyst phenylhydrazin was used. Measurements were made with standard Dreyer pipettes.

Eight tubes were taken and set up as follows:

No. of tube.	Serum.	Hemoglobin.	Phenylhydrazin.
1	Patient	Patient	0
2	Patient	Patient	+
3	Patient	Normal	0
4	Patient	Normal	+
5	Normal	Patient	0
6	Normal	Patient	+
7	Normal	Normal	0
8	Normal	Normal	+

In each tube 30 drops of serum and hydrogen sulphid solution and 4 drops of red blood cell suspension were used; phenylhydrazin was added by dipping a straight wire a definite distance into the fluid. Sterile technique was followed.

After mixture by shaking, the tubes were incubated at 37° C. and at measured times 1 or 2 drops were removed by pipette and examined. The experiment was repeated three times using different normals. The result was the same except that the time varied by a few minutes in the three tests. In tubes 2, 4, 6 and 8 a spectrum of sulphemoglobin appeared at exactly the same time.

If the serum of the patient had contained reducing substances, tubes 2 and 4 should have shown the spectrum first; if the hemoglobin of the patient had a special affinity for sulphids, tubes 2 and 6 should have shown the change first.

The evidence of hepatic deficiency is based on the following findings: Consistently high values of urinary uric acid; the presence of creatin in the intermenstrual urine whenever sought; the consistently high values of urobilin in the urine and the levulose tolerance test which gave the following result, 0.092, 0.106, 0.133, 0.142, 0.140, 0.100 gm. per cent. The diet which was given has been found useful in hepatic deficiency;[5] a very similar diet was found to be effective by Long and Spriggs in their case. This diet, now called a high carbohydrate diet is simple, the patient receives no fat, milk included as fat, and only the basal requirement of protein; carbohydrates are allowed freely.

Discussion and Review of Cases. Including the case of sulphemoglobinemia described by Mason and Conroy[6] in 1921, 14 others were known up to that time. A doubtful case is described by Jamieson[7] in 1919. Since then Hijmans van den Bergh[2] has reported 5 cases all associated with fecal retention; Snapper,[8] 2 in which phenacetin had been taken for a long time; Parsons[9] and Willemse[10] each report single cases in infants and Vogel[4] has recently described a case following intoxication with para-amido-phenol.

Van den Bergh has proposed the name Autotoxic Parhemoglobinemia for this group of conditions in which cyanosis is independent of anoxemia. He describes four groups:

1. Nonhemolytic methemoglobinemia, blood plasma free of the pigment; cases of enterogenous cyanosis, acetanilid and other analgesic poisonings and mild poisoning from nitrites fall into this group.

2. Nonhemolytic sulphemoglobinemia, the disease under discussion, plasma free of the pigment.

3. Hemolytic methemoglobinemia, in which the plasma shows the pigment. This occurs in poisoning with potassium chlorate, in 1 or 2 cases of eclampsia and in a very few cases of septicemia due to anërobes.

4. Hemolytic sulphemoglobinemia, with free pigment in the plasma, 1 or 2 cases only, due to anërobic sepsis.

The etiology of the primary sulphemoglobinemias is obscure; in van den Bergh's series fecal retention appeared to be the cause and his series shows differences from the true idiopathic cases. In the cases of Snapper and Vogel, intoxication with known substances is blamed. The remaining cases have not been adequately explained.

An early suggestion was that the condition was due to the combination of the hydrogen sulphid, normally present in the bowel, with hemoglobin. This leaves unexplained why sulphemoglobinemia is rare, but the relatively numerous cases due to fecal retention should not be ignored. However, few cases of fecal retention show this syndrome.

It has been found that certain reducing substances facilitate the fixation of sulphids to hemoglobin, and that very small amounts of these substances are necessary.[1] MacKenzie Wallis found that reducing substances were present in the blood of the cases he investigated;[11] he considered that they were hydroxylamin derivatives of protein decomposition, split off by a nitroso bacillus which he found in all his cases. Against this very attractive theory there are certain objections: The organism will not grow at body temperature but only at 25° C., also that neither this organism nor its products could be isolated in the cases specially examined since.[3, 6, 9] I did not try to isolate this organism in this case; the fact that it cannot grow at body temperature appears to disqualify it. Moreover, its products were sought and not found. Nitroso bacteria are common vegetable saprophytes and symbionts and their presence in the alimentary tract is not astonishing.

That reducing substances are of importance in some of the cases cannot be denied; van den Bergh has also found them present. In addition he noted that the blood of patients taking Apenta water and those being treated with sulphur, sometimes showed a faint spectrum of sulphemoglobin; also that the ease of production of the spectrum varied in different individuals and suggested that the liver might be responsible for the difference.

During the investigation of this case two facts arrested attention: it is known that hydrogen sulphid administered per rectum is relatively innocuous[12] and, second, that sulphemoglobin is found in the blood after death. The first suggests that there is a detoxicating function in the portal territory for sulphids; the second that either reducing substances appear during decomposition allowing fixation of sulphids, or, that this fixation is due to the absence of the detoxicating function noted.

The fate of sulphids obtaining entry into the blood is not fully known; some are converted into hydrogen sulphid which is ventilated out, *via* the lungs; some are broken down and probably oxidized to sulphates.[13] Ingested sulphur is eliminated by lungs,

sweat glands, urine and feces; the metabolism of sulphur is little known.

Experimental Production of Sulphemoglobinemia. This conception of a detoxicating function for sulphids in the liver suggested an attempt at experimental production. Van den Bergh had already found that sulphemoglobin appeared in the blood of rabbits after administration of large amounts of sulphur by stomach tube; previously Lewin[14] had found the same for dogs. These findings do not help much, for sulphur is still given in large doses in several diseases, but the disease under discussion remains rare.

Two groups of rabbits of 6 each, all of about the same weight were taken. The one group was for control, the other was given repeated intravenous injections of Novarsenobenzol in maximum sublethal doses. Both groups received a vegetable paste containing 0.25 gm. of sulphur per day; the treated group also had 1.8 gm. of casein per day in order that the metabolism of this foreign substance might further embarrass the liver.

An epidemic of diarrhea somewhat interfered with the experiment and some of the animals died but were replaced. The mortality was no greater than among the laboratory stock. The liver of the treated animals showed well-marked parenchymatous degeneration, and some showed evidence of reparative processes but space does not permit details. Those of the untreated group which succumbed showed no abnormality.

Of the treated rabbits 7 were examined satisfactorily before death for sulphemoglobin and of these 4 showed its presence; 2, at thirteen and 2, at twenty-nine days. Among the controls, receiving the same amount of sulphur, no sulphemoglobin was found. It is possible that a larger proportion of the treated rabbits would have shown the condition if a longer time had been possible; 2 out of the 7 had only been treated for two weeks when the experiment had to be concluded.

Van den Bergh has reported that about 20 per cent of the bloods of his untreated laboratory rabbits show faint spectra of sulphemoglobin. I have examined 25 rabbits of this laboratory, but have only found it in those noted.

It is suggested that this experiment tends to show that the liver is of importance in detoxicating sulphids passing to it in the portal blood and that in certain cases of hepatic deficiency this function is in abeyance. The relatively large proportion of cases in fecal retention may be explained by an easy assumption that the liver had been damaged by the excess of toxic substances carried to it in such cases. In the other cases due to the use of drugs, the present included, the same hypothesis is feasible. It will be of interest to know the results of hepatic tests in subsequent cases of the idiopathic type. It may well be that the explanation of the finding in rabbits noted by van den Bergh is hepatic disease; a large number

of the rabbits, in this country at least, show hepatic disease in the form of coccidiosis.

This conception of the importance of the liver gives the treatment of these cases; remove any toxic factor which can depress the liver and give a diet which will not throw much work on its digestive functions. Even then cure will be slow, for it has been found that sulphemoglobin is excreted slowly.

Summary. 1. A case of sulphemoglobinemia following prolonged use of commercial headache powders is described.

2. The condition slowly cleared up on a diet which spared the liver. When proposals for discharge were made, a surreptitious use of the headache powders led to attacks of methemoglobinemia.

3. No abnormal reducing substances were found in the blood and the blood was found to fix sulphids no more readily than controls.

4. Hepatic deficiency was proved to be present.

5. Experimental injury to the livers of rabbits was followed by the appearance of the pigment in the blood; controls were negative.

6. It is suggested that, among its many other functions, the liver detoxicates sulphur compounds ascending in the portal blood.

I am indebted to Prof. I. Walker Hall for laboratory accommodation and help and to Dr. C. E. K. Herapath for the notes on the clinical condition of the patient; a grant from the Colston research fund has paid the expenses of this research.

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SICKLE-CELL ANEMIA.

Report of an Active Case.

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In 1910, Herrick[1] first called attention to a peculiar change in the shape of the red blood cells of the blood in a severe case of

anemia. He described these erythrocytes as assuming an elongated or sickle shape.

Since that time, Washburn,[2] Cooke,[3] Meyers,[3] Mason,[4] Sydenstricker,[5] Huck,[6] Emmel,[7] and others have described practically the same change in the shape of the erythrocytes in certain severe cases of anemia. Gradually a chain of symptoms and signs were worked out in this type of anemia. This peculiar distortion of the red blood corpuscles is the most constant feature so far observed in this form of anemia; so it seems appropriate, for the present at least, while our knowledge concerning this condition is so meager, to call it "Sickle-Cell Anemia."

Etiology. The real cause of sickle-cell anemia is unknown. There is much proof that the disease is familial in type as shown by Emmel, Washburn, Huck, Sydenstricker and others. Sydenstricker points out that the dyscrasia is transmitted according to the Mendelian law and manifests itself as a dominant characteristic. The cases so far reported have been limited to the negro race.

Symptoms. As to the symptoms, one can do no better than quote Sydenstricker, as he has probably observed more cases than any one who has written on this subject. "The disease is recognizable in two phases which we have termed active and latent, according to the condition of the blood and the severity of the symptoms. In the active phase, anemia is pronounced and many of the symptoms, especially dyspnea, palpitation, and weakness are referable to it. Pain, arthritic and muscular, without evidence of inflammation, is constant. Epigastric pain after eating and recurrent attacks of epigastric and left hypochondriac pain have been present in most cases and vomiting may occur. There is fever of low grade and night sweats are common. Exacerbation of these symptoms occur at intervals, so that the history is one of remissions and relapses. Leg ulcer is a common complication.

"In the latent phase, patients presenting no symptoms of anemia, on questioning will give a history of rheumatic attacks, pain in the epigastrium and left hypochrondrium, and periods of weakness and dyspnea which have been separated by years of normal health."

Physical Signs. The most characteristic physical signs noted during the active state are: Poor development, greenish discoloration of the sclera, hypertrophied tonsils and general lymphadenopathy with the exception of the spleen which is atrophied in most cases, enlargement of the heart with acceleration of the heart rate, low blood pressure, atrophy of the genitalia, and ulcers of the extremities. In addition to the signs mentioned above, the patient about to be reported showed marked mental disturbance. His response to questions was slow and he seemed to take no notice of his surroundings. He was irritable and wished to be left alone. During the latent stage, there may be few or no signs other than the sickling of the red cells and the greenish discoloration of the eyes.

Blood. Red blood cells vary between 1 million to 5 million, the lower number being found in the active cases and the higher in the latent cases. The hemoglobin varies with the cell count. The majority of cases reported show a comparatively high color index usually slightly less or very closely approaching 1. However, in the case under observation, the color index has been quite low, varying from 0.6 to 0.7. The leukocytes are almost invariably increased in number, varying from 11 to 64 thousand. (Sydenstricker). Platelets are moderately increased in the majority of cases studied. A few myelocytes are present in most examinations.

Emmel was the first to make an extensive study of the fresh blood in cases suffering with sickle-cell anemia. He found when fresh blood was drawn and placed on a glass slide, a cover slip applied and sealed with petroleum jelly, the red blood corpuscles underwent a peculiar transformation in shape. They assumed elongated, crescentic, or sickle shapes. This change in shape of the erythrocytes is observed in only a few cells when the blood is freshly drawn; but in twelve to twenty-four hours after it is drawn, from 60 to 95 per cent of the red cells show this change in shape. After the blood has stood for forty-eight to seventy-two hours, the red blood cells return to their normal shape.

This peculiar phenomenon which takes place in fresh blood is the most characteristic feature of the disease under discussion. Graham, Sydenstricker and others have tried to explain the factors involved in sickling of the red cells but so far have been unsuccessful. They are of the belief that the cause of the phenomenon lies with the red blood cells, although the serum also plays a part. When red cells from a case of sickle-cell anemia are washed and suspended in normal salt solution, they will not sickle; but if serum from a normal individual is added, they will become sickle shaped. On the other hand, red cells from a normal individual will never sickle when placed in serum from a patient with sickle-cell anemia. Bile or bile pigment added to serum hastens the sickling of red blood cells.

Graham[8] has noticed in one of his cases that preparations made one day may show no sickling and preparations made, as far as it was possible to tell in exactly the same way the following day, showed progressive sickling. He further noticed on one day, one of three preparations failed to show sickling although all three had been prepared, so far as could be determined, in exactly the same way.

Graham further noticed that erythrocytes fixed in Zenker's fluid showed no deformity; while those fixed in 10 per cent formalin from the same tissue showed marked sickling.

The case herein reported was in the hospital six weeks and fresh preparations were made on four or five different occasions, but no progressive sickling observed; however, two weeks after his discharge, we were able to get him back to the laboratory for another

fresh blood preparation study, and found, after twenty-four hours that 90 to 95 per cent of the erythrocytes showed sickling in three separate preparations. These specimens of blood were examined daily for one week and there was no evidence of any return to their original shape until the eighth day. By the tenth day, with the exception of about 10 per cent, all had returned to their original shape.

A second study was made two weeks later and the same phenomenon was repeated: namely, prompt sickling and slow return to normal shape. Exactly the same technique was used in preparing the blood for study while the patient was in the ward as when he was an outpatient. We are at a complete loss to say what caused the phenomenon to be present at one time and absent at another.

The reticulocytes are increased during the active stages and naturally depend on the rate of blood destruction and activity of the bone marrow. The van den Bergh test has been positive in cases of active anemia. Sydenstricker has described a condition which was found in the case under discussion: namely, immediately before remission, normoblastic crises occur; and after remission sets in, sickle cells may almost disappear from the circulating blood. Large mononuclear leukocytes, phagocytic for erythrocytes, are found in stained smears and fresh preparations.

Pathology. The most striking pathologic change is in the red blood cells of the body. The peculiar change in shape of the red blood cells is observed most strikingly in fresh blood preparations which have stood for twenty-four hours; but some socalled sickling of the red cells may be seen in cover slip preparations fixed and stained with Wright's stain; and as has been previously stated, a few sickle cells may be seen as soon as it is drawn. Hypertrophy of lymphoid tissue has been constantly observed in those cases going to autopsy. The spleen, however, is found to be atrophied and shows areas of hemorrhage and old scars. The bone marrow shows evidence of hyperplasia and a striking change in the shape of red blood cells have been observed. The liver is increased in weight and shows a deposit of a brown iron-free pigment. This pigment was observed by Sydenstricker in the liver, spleen, kidney, and endothelial cells. Large phagocytes are present in the spleen and blood stream. The progressive anemia, increase of bilirubin in the blood, and pigmentation of the tissues would indicate active blood destruction. The presence of urobilin in the urine would suggest liver damage.

Report of Case. R. J., a negro boy, aged thirteen years, a native of Pennsylvania, who was never out of the state, was admitted to the children's ward of the Conemaugh Valley Memorial Hospital on July 20, 1925, on the service of Dr. H. J. Cartin, with a chief complaint of weakness, headache, incontinence of urine.

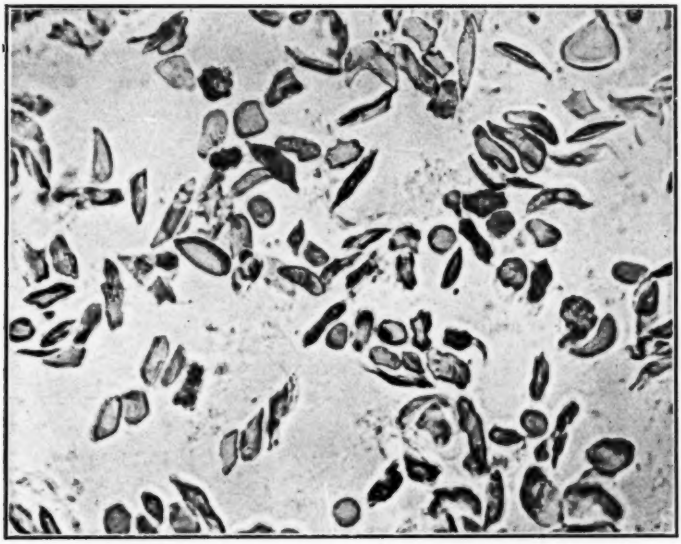

FIG. 1.—Fresh preparation from R. J. Blood forty-eight hours old.

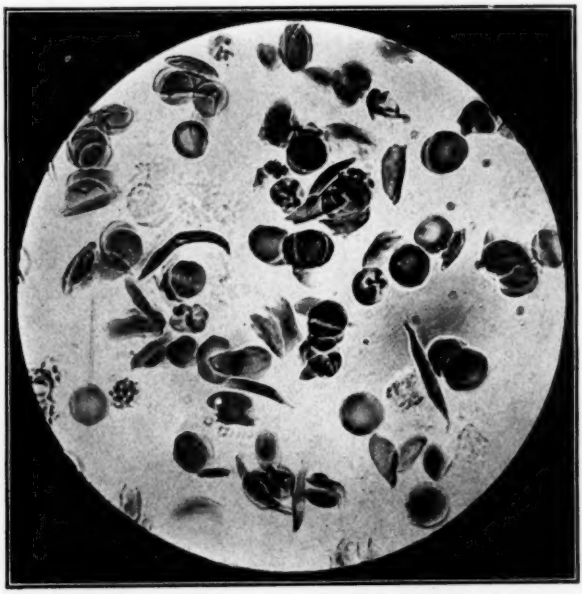

FIG. 2.—Fresh preparation from severe active case. (Sydenstricker.)

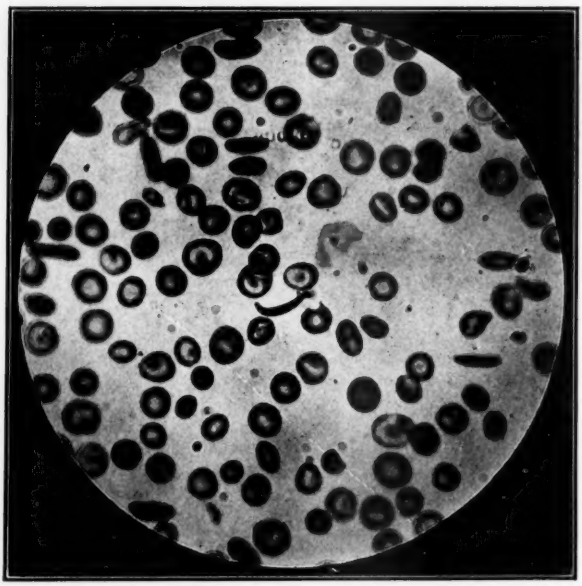

FIG. 3.—Stained blood smear from active case with well-defined sickle cell in center.
(Sydenstricker.)

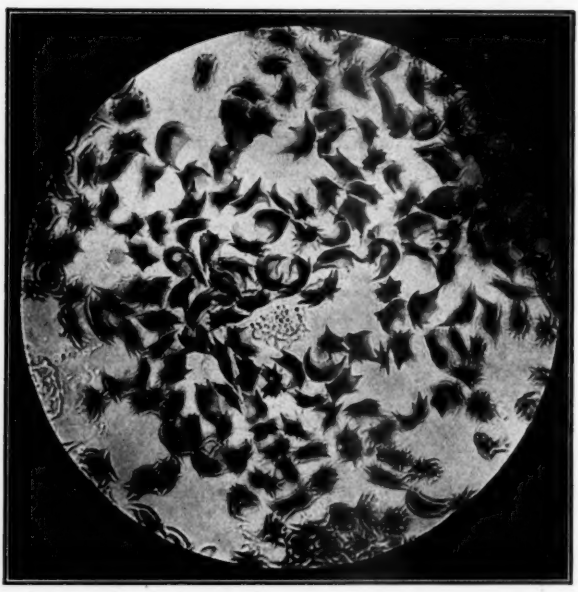

FIG. 4.—Fresh preparation of blood from latent case after eighteen hours.
(Sydenstricker.)

Family History. The father and mother and one sister and one brother are living and apparently well. The father and mother separated several years ago, at which time the mother took one boy and moved to West Virginia. The father, who is a coal-black negro, enjoys excellent health and examination of his blood revealed no evidence of sickle-cell anemia. The twelve-year-old sister is very well nourished and apparently enjoys good health; but when a specimen of her fresh blood was examined after twenty-four hours, 50 to 75 per cent of the red cells were sickled or showed the bizarre distortion so characteristic of this anemia. In every other respect, her blood picture was normal. She is unquestionably a latent case of sickle-cell anemia. There is no history of tuberculosis, diabetes, malignancy, insanity, nor blood dyscrasias in the family.

Past History. He had childhood diseases, including whooping cough; also pneumonia twelve years ago and sore throat frequently. He never had scarlet fever, diphtheria, chorea, operations, snuffles or skin rash. He has had incontinence of urine since birth.

Present Illness. On Friday, July 17, 1925, the patient went to bed complaining of weakness and headache. This did not seem to have any relation to any food ingestion. He has not been nauseated and does not vomit. He has headache, and some dizziness, but no blurring of vision or diplopia. He does not cough or expectorate, but sweats excessively during the night. He has lost about 10 pounds in the past month. There is no precordial pain or distress, no cyanosis or edema. He has palpitation, especially after exertion. There is no nausea or vomiting, and the appetite is fair. There is no abdominal pain or tenderness, no liver pains, no jaundice, and the bowels are fair. He has been incontinent since birth, but has no polyuria, hematuria, or dysuria; he voids three times during the day and twice at night. He has occasionally had some pain in the knees, but was never confined to bed with the joint pains.

Physical Examination. The patient is a fairly well-nourished negro boy apparently thirteen years of age, resting comfortably. The scalp is negative, without nodes or scars. The pupils are equal and regular and react to light and in accommodation. The scleræ are jaundiced. The ears and the nose are negative. The tonsils are slightly hypertrophied, the pharynx negative, the mucous membranes pale. The teeth are fair; the tongue is coated, and the breath fetid. A visible pulsation is present in the upper portion of the neck. The chest is symmetrical, expansion equal and there are no apparent signs of rickets. The glands in the axilla are palpable. The apex beat is seen and felt in the sixth interspace, left mammary line. There is apparently some cardiac enlargement. Heart measurements are as follows: The right border is found in the fifth interspace, 5½ cm. to the right of the midsternal line and the left border is found 11 cm. to the left of the midsternal line.

The heart sounds are regular, indistinct, and of poor quality and there is a systolic murmur over the aortic and pulmonary regions. The blood pressure is systolic, 85; diastolic, 20. The lungs are negative; no rales or friction sounds. Voice and breath sounds are normal, the abdomen shows no masses, no rigidity, nor spasm. There is tenderness over the splenic region. Liver and spleen are not palpable, and there is no renal pain or tenderness. Genital and rectal examination are negative. The extremities are negative, no edema, scars, eruptions, nor varicosities. The mentality is poor, thought sluggish; he says little, and wears a very dull facial expression.

Progress of Case. The patient gradually improved while in the hospital. At the end of the first week, he began to notice and talk to the other children in the ward. His appetite became better and he gained some weight. On September 4, 1925, he was so much improved that he was allowed to go home. He has been attending school every day since his discharge from the hospital.

Laboratory Findings. Shortly after admission to the wards, we suspected the patient of having sickle-cell anemia; so a fresh blood smear was made and sealed with cover slip and vaseline, but after waiting twenty-four hours, and then forty-eight hours, we found no progressive sickling. There were a few sickle-shaped cells noted in the slides stained with the differential stain and a very few noted in the fresh blood as soon as it was drawn, but the writer felt this was not sufficient evidence to make a positive diagnosis. On four different occasions following this, we made fresh blood preparations and each showed a few, possibly ½ to 1 per cent, sickle cells when drawn, but his number did not increase on standing. Finally, a stained preparation of blood was sent to Dr. V. P. Sydenstricker, who confirmed our diagnosis, and, as has been stated before, on October 20, November 3, and November 28, we have had this patient return to the hospital laboratory for an examination of his blood and on each occasion the fresh blood on standing twenty-four hours has shown from 90 to 95 per cent sickling.

BLOOD COUNTS.

Date.	Red blood cells.	White blood cells.	Hemoglobin per cent.	Color index.
July 22	1,168,000	15,300	10	0.4
July 28	1,376,000	22,800	10	0.3
July 29	1,440,000	10,000	18	0.6
August 3	1,520,000	9,400	18	0.6
August 10	1,504,000	11,200	25	0.6
August 12	2,272,000	8,850	27	0.6
August 17	2,122,200	9,200	29	0.6
August 26	2,016,000	10,000	26	0.6
September 3	1,912,000	10,150	21	0.5
October 20	2,100,000	15,000	25	0.6
November 3	2,400,000	23,000	30	0.6
November 24	2,100,000	15,700	25	0.6

The differential counts showed from 50 to 60 per cent polynuclears, 10 to 15 per cent lymphocytes, 1 to 5 per cent myelocytes, 3 to 4 per cent eosinophiles, and 5 to 15 per cent large mononuclears. Hemoglobin determinations were made with the Dare hemoglobinometer which may partially account for the low color index. Stained preparations of blood showed about 1 per cent of the red cells were sickle shaped. A blood culture taken on admission was negative after three weeks incubation.

On July 23, 1925, a differential slide showed, as most specimens examined, very few nucleated reds, while a specimen taken July 25, 1925 showed from ten to fifteen nucleated red corpuscles for every hundred leukocytes.

On November 3, 1925, the patient showed 6 per cent reticulocytes, 400,000 platelets, and a coagulation time of five minutes. The van den Bergh test showed four parts to 100,000 bilirubin, and a slight reaction by direct method was noticed. The resistance of the erythrocytes to hypotonic salt solution was slightly greater than normal. Hemolysis began at 0.35 and was complete at 0.2.

Roentgen ray examination of the heart, on July 23, showed questionable enlargement. Blood and spinal fluid Wassermann reactions were negative. Stool examination for ova and parasites was likewise negative. Electrocardiogram showed a P–R interval of eighteen hundredths second. Amplitudes of both R and T waves are increased in Leads I and II.

COMMENT. The report of this case is interesting for the following reasons: It is the first case reported in Pennsylvania; it occurs in a negro boy who has spent his entire time in this state; it bears out the thought that the disease is familial in type and is not a tropical disease. The report of these cases should stimulate a more extensive search and study of similar cases in an increasing northern negro population as well as among southern negroes.

Summary. 1. Sickle-cell anemia is a comparatively new disease which we shall have to class with the hemolytic anemias.

2. The most characteristic feature of the anemia is its sickling phenomenon which is not constant.

3. A diagnosis can be made from stained-blood smears, although the progressive sickling observed in fresh blood after twenty-four hours is the most diagnostic feature.

4. Latent cases of sickle-cell anemia show a greenish discoloration of sclera and the sickling phenomenon but no other striking blood changes.

5. The case reported in this paper is unique in that it occurs in a negro boy born and reared in Pennsylvania, in that the color index is low, and in the fact that during the first six weeks the case was under observation in the hospital we were unable to demonstrate a progressive sickling of the fresh blood, and later, when we were able to obtain the sickling phenomenon, the red cells retained their bizarre shape for seven to eight days.

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HYPERTENSION.

Clinical Aspects of the Etiology and Therapy.

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and

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Arterial hypertension *per se* is but a symptom of vascular disease, but a most important symptom inasmuch as it is a constant menace to the unfortunate patient. As a symptom it is an indicator of progress toward improvement or exacerbations, if all other factors, particularly cardiac efficiency, are equal.

Numerous theories have been presented concerning the etiology of vascular disease with hypertension. Among the earliest was the conception that vascular disease was due to nephritis, an idea which arose as a result of the frequent coincident presence of both diseases. Both Foster[1] and Klotz[2] have recently reëmphasized the point that the two processes are coincident but not dependent upon each other. Heredity has long been known to play some role.[3] Infection of various sorts has been considered responsible for hypertension. The relation of syphilis to hypertension is unsettled. Walker and O'Hare[4] find less hypertension among syphilitics than among control cases, but Thom[5] reports a 50 per cent incidence of hypertension among a large number of luetics. Infections of the bowel or intestinal stasis have been considered of great moment by a number of investigators,[6] and the improvement following the use of a limited dietary is considered to be a result of altered intestinal flora. High-protein diet has recently been emphasized as an important etiologic factor in hypertension by Newburgh and Clarkson[7] Nuzum, Osborne

and Sansum[8] and others,[9] but Strouse and Kelman[10] have presented evidence to the contrary. Intoxications from metabolic products, particularly the split products of protein digestion, have recently been shown to be of considerable significance. Longcope[11] some time ago pointed out the importance of anaphylactic phenomena in connection with vascular and renal disease. Major,[12, 13, 14] McDonald[15] and others[16] have recently demonstrated the marked pressor effect of guanidine bases and the protective effects of tissue extracts as first suggested by Oliver and Schäfer.[17, 18] Major[19] incriminated the guanidine bases as marked pressor substances with very clear experimental data. Similar findings have been presented by Dale and Dixon,[20] Barger and Dale,[21] Harvey[22] and Clark.[23] It has been shown that these substances are detoxicated by hepatic perfusion.[24] Hypercholesterolemia has been considered as an etiologic factor, Westphal[25] finding an excess of cholesterol in the blood of 71 per cent of a series of hypertension cases.

The anatomic basis of hypertension has recently received close attention through the work of Fishberg[26, 27] and Jaffe,[28] but the very lack of uniformity in the pathologic changes as revealed by their work on the arterioles prohibits any conclusions anent the etiologic mechanism. One further conception of moment has been presented: namely, that a metabolic disorder, associated with endocrine dysfunctions of various types and a diminished blood-calcium content, is responsible for many cases of hypertension. It has been thought that the lowered calcium content led to a condition of increased vasomotor tonus and irritability. The conception was suggested both by Reid[29] and Kylin.[30]

The above brief résumé of the chaos that exists concerning the etiology of hypertension deals with but a small part of the voluminous literature. In all probability the etiology of vascular disease varies in different cases, and may be attributed to various factors of varying importance. This idea has been previously emphasized by Christian,[31] Piersol[32] and Faught.[33] The most important etiologic factors in vascular disease may be tabulated as follows:

1. Hereditary Influences.
2. Infection (past or present).
   - I. Generalized systemic infections.
   - II. Focal infections with dissemination of organisms.
   - III. Focal infections with dissemination of toxins.
   - IV. Syphilis.
3. Intoxications (noninfectious).
   - I. Exogenous.
     - (*a*) Heavy metals (lead, arsenic, etc.).
     - (*b*) Alcohol.
     - (*c*) Dietary: Condiments and spices; excesses of any food; excesses of meats and meat extractives; constipation.

II. Endogenous.
(*a*) Metabolic.
1. Pregnancy.
2. Fatigue.
3. Endocrine disturbances.
(*b*) Split products of protein cleavage.
(*c*) Anemia.

In order to study the relative importance of the various etiologic factors as outlined above, an analysis of 121 consecutive cases of hypertension from the service of Dr. W. E. Post at the Presbyterian Hospital, Chicago, was undertaken. The average age of these patients was 52.1 years. Of the 121 cases, 11 were discarded because of insufficient data. The remaining 110 were just evenly divided between the two sexes, 55 being males and 55 females. Factors of etiologic significance appeared with the following incidence:

	Cases.	Percentage.
Dental infections	67	60.8
Tonsillar infections	39	35.4
History of familial vascular disease	35	46.6
No family history	35	46.6
Syphilis	14	12.6
Excessive fatigue	29	26.3
Sinus infection	4	3.6
Pyelitis or cystitis	11	10.0
Acute nephritis	2	1.8
Chronic pharyngitis	8	7.3
Toxic goiter	3	2.7
Some focus of infection	91	82.7

The most conspicuous diseases found in the past histories of these patients were:

	Cases.	Percentage.
Rheumatism	12	10.9
Typhoid fever	11	10.0
Cholecystitis	5	4.5
Pneumonia	5	4.5
Scarlet fever	5	4.5
Sinus infection	5	4.5
Acute renal disease	4	3.6
Toxic pregnancies	9	16.0 (of women)

A similar analysis of the cases under forty-five years of age revealed essentially similar findings. There were 33 such patients, and of these 19 were males and 14 females.

	Cases.	Percentage.
Dental infection	20	60.6
Tonsillar infection	13	40.0
Some head focus of infection	28	84.4
Typhoid fever	6	18.0
Syphilis	5	15.1
Past sinus infection	9	27.2
Familial hypertension	13	46.4
No family data	5	....
Toxic pregnancies	7	50.0 (of women)
Of these, foci of infection also present	5	71.4
Excessive fatigue	13	40.0
Acute nephritis	2	6.6

The above statistical study presents the multiplicity of etiologic factors as found in a series of cases. By far the most frequent and important factors found are foci of infection somewhere about the head, particularly dental, tonsillar or chronic nasal infections. A history indicating a familial tendency to arterial disease is frequently encountered. The incidence of a history of past pregnancies with unusually marked toxemia in women with hypertension is high. Apparently syphilitic and acute renal disease are not frequent causative factors. Regarding past illnesses, rheumatic infections and typhoid fever appeared most commonly. Fatigue, particularly when the result of a long continued mental or physical strain was noted in the histories of a considerable number of these patients.

Summarizing the above data, we feel that the following conclusions are warranted: The etiology of vascular disease with socalled essential hypertension is not uniform, varying with different cases. Past and present infections, particularly those which tend to become chronic and focalize are the most conspicuous causative factors, while hereditary tendencies and contributory intoxication such as the toxemia of pregnancy and excessive fatigue play important roles. In any one given case a combination of several factors may usually be found after careful study of the situation.

The above conception of the etiology of hypertension led to the formulation of a method of therapy based upon the following general principles: (1) Careful history taking with particular search for evidences of past sources of vascular injury; (2) search for any present or recent foci of infection; (3) elimination of such foci whenever possible; (4) elimination from the diet of meat extractives such as broths, gravies and meat soups, but not of meat, boiled meat being permitted two or three times per week, limiting the protein to approximately metabolic requirements; (5) complete elimination from the diet of condiments and spices containing irritating volatile oils such as pepper, mustard, catsup, horseradish, onions, and the like; (6) the encouragement in the use of bland fluids up to three liters per day, such fluids consisting of water, milk, fruit juices, bland carbonated beverages, and coffee or tea in the morning only; (7) the use of sodium bromide in doses of 10 to 15 gr. three times per day, together with advice to arrange a daily program in which work is interrupted by periods of rest. No other therapeutic measures were employed except as indicated by complications.

An opportunity to determine the efficiency of the above method of management presented itself in the Renal Disease Clinic of the Central Free Dispensary associated with Rush Medical College of the University of Chicago, where 109 unselected consecutive cases of hypertension have been taken care of in the two years 1923 to 1925. These cases all presented themselves with a systolic vascular tension

of 150 mm. or over or with a diastolic pressure of over 100 mm. or both. In all cases the management has been essentially the same, the only drug used being the mild sedative, sodium bromid, in moderate divided doses. In those cases presenting cardiac decompensation, digitalis was of course employed.

Of the 109 cases treated only 87 are of value for analysis of the therapeutic results as the other 22 had been under observation too short a time. The average duration of observation for the 87 cases studied was 7.5 months, with a maximum of forty-eight months and minimum of one month. Only a few cases who were seen less than two to three months are included in this series. Men comprised 29, or 33.3 per cent, of the group and women 58, or 66.6 per cent. The average age for the whole group was 52.3 years, the ages ranging from nineteen to seventy-two years. The average age of the men was a little greater than that of the women, being fifty-four years in contrast with fifty-one years. Of these 87 cases, 77, of 88.5 per cent, improved both subjectively and as regards the degree of hypertension, 7, or 8 per cent, became worse, and in 3, or 3.5 per cent, no change in the condition was noted.

The total average arterial tension of these cases on admission to the clinic was systolic, 200 mm.; diastolic, 123.7 mm. At the close of the period of observation the total average for the whole group, including the patients who failed to improve, was systolic, 164.4 mm.; and diastolic, 97.7 mm.; showing an average improvement of 35 mm. systolic, and 26 mm. diastolic pressure. This improvement is one of 17.7 per cent of the original systolic tension and 15.7 per cent of the diastolic. When one considers the average age of this group, the great economic difficulties and poor coöperation present in a dispensary clientele, and that the patients were ambulatory and the majority of them working, the therapeutic results are good. Unusually poor coöperation was remarked in the histories of 15, or 17.2 per cent.

Coincident complications were of course frequent in such a group. Clinically evident chronic nephritis was present in 20, or 23 per cent, chronic degenerative myocarditis in 20, or 23 per cent, and oral sepsis in 12, or 13.8 per cent. Some form of focal infection was found in 47, or 54 per cent. Chronic rheumatism was present in 11, or 12.6 per cent, and colitis or marked constipation in but 11, or 12.6 per cent. Obesity was noticeable in but 10, or 11.5 per cent, and syphilis was demonstrated in only 5 cases, or 5.7 per cent.

The use of sodium bromid in these cases is based upon the conception that rest, mental as well as physical, is of very great importance. Foster,[34] Becchini[35] and du Bray[36] have all emphasized the importance of rest. The bromid as a diffuse, mild sedative permits these people really to relax when resting physically instead of keeping up a continuous mental restlessness and anxiety. Whether there is a direct sedative action upon the nervous vaso-

motor mechanism is problematical. Mosenthal[37] has recommended chloral hydrate in small doses on the same basis.

Mosenthal[37] finds that moderately liberal protein feeding does not increase the arterial tension, but urges the reduction of the patients weight in obese individuals. Wiseman[38] has shown that one form of meat is no more injurious than another. In an effort to avoid protein starvation, approximate protein requirements were permitted in the dietary, but fats and carbohydrates were limited to reduce weight. Meat has been allowed two or three times per week. The patients are instructed that boiled meats without the gravy are the least injurious, for the high salt and extractive content of meat broths, soups and gravies is felt to be a vascular and renal irritant.[39] Reduction in meats and protein was most strongly urged in those cases where habitually large amounts of meat were formerly taken.

The removal of foci of infection is felt to be of great importance. This is usually the most neglected part of the therapy. The importance of lowering the blood pressure to reasonable levels cannot be overestimated, but too radical lowering with violent transient vasodilators has no prolonged beneficial effects and may be exceedingly dangerous as the sclerotic cerebral vessels require an increased pressure to maintain their circulation. In no instance have we used nitrites or other drugs for purely temporary symptomatic relief. Because of the ambulatory nature of the patients in this group, blood letting and sweating have not been employed. Because of the variability in blood pressure in patients with hypertension, these patients have all been watched several months before any conclusions were drawn.

Summary. Arterial hypertension, as a symptom of vascular disease, may be due to one or more of several etiologic factors. Of these factors those most frequently encountered are foci of infection, past or present, intoxications of endogenous or exogenous origin, excessive fatigue, and an apparent hereditary vascular instability. The treatment of hypertension by the removal of sources of infection, rest, improving elimination by increasing the fluid intake, but not by drastic catharsis, and the use of mild sedative doses of sodium bromide has given unusually good results over a moderately long period of observation. At present studies are being carried out in connection with the metabolism of calcium in hypertension and it is our hope to be able to compare other methods of therapy on the same basis.

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RETROGRADE CAPILLARY PULSATIONS IN HEART FAILURE.

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The capillary pulsations previously described in medical literature have dealt solely with centripetal ones, that is, those conducted from the arterioles to the capillaries. These produced either an alternate paling and flushing of the skin (macroscopic capillary pulse), or an intermittent bloodflow in the capillaries observed microscopically (microscopic capillary pulse). A retrograde capillary pulsation, one coming from the venules back into the capillaries has not yet, as far as I know, been described. Such was the case in a patient upon whom capillary studies were made.

The patient, Mrs. M., aged thirty-four years, sought medical aid because of dyspnea and palpitation even on the slightest exertion. Nocturnal paroxysms of dyspnea were troublesome. She had an acute respiratory infection (influenza?) two years ago and since that time her symptoms have been very distressing.

The cardiac dimensions were 7 cm. to the right and 9 cm. to the left, a predominent right-sided dilatation. There was a reduplication and an accentuation of the second pulmonic sound. Premature beats were heard, also a few dry rales over the bases of the lungs. There was tenderness in the liver region denoting congestion of this organ, although the free edge could not be palpated. Her face was flushed and it had a cyanotic hue. No murmurs were heard on the first examination.

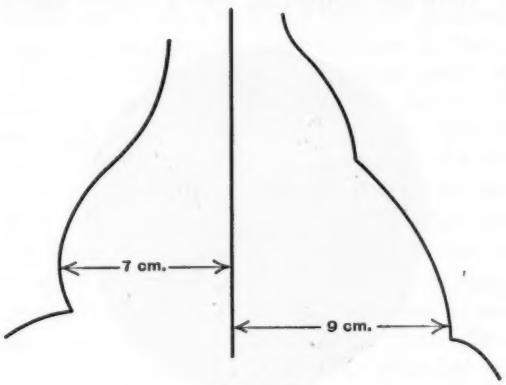

FIG. 1

After two days of rest in bed and digitalis therapy, a short presystolic rumble became audible at the apex and in addition a blowing systolic murmur was heard in the region of the ensiform cartilage. It was transmitted for about 2 inches to the right of the sternum. Because of the characteristics of this murmur, tricuspid insufficiency was assumed to exist. The second pulmonic sound was not so loud as on the first examination; probably because of a lessening of the pressure in the pulmonary artery following the tricuspid regurgitation. No liver pulse was discernible. The teleroentgenogram (Fig. 1) showed bilateral cardiac enlargment, with dilatation of the pulmonary artery and left auricle.

The case was clearly a mitral stenosis with heart failure, probably associated with a tricuspid insufficiency.

The capillaries of the skin were visualized by the Lombard[1]-Muller-Weiss,[2] method which is as follows:

A drop of oil is placed on the skin of the hand and the area so treated is examined with the microscope under a strong light. A 40-watt electric bulb with a condensing lens placed close to the

microscopic objective does very well for this purpose. One may in this way readily see the capillary tufts scattered through the field. Most of these tufts come up from the deeper parts of the dermis, fold over and return so that only a small part of the capillary loop can be brought into focus. Under such conditions it is scarcely ever possible to see the corpuscular flow. Occasionally a capillary may be found which, arising from the depths of the dermis, turns at right angles and takes an horizontal course for a short distance, and in such a case, under favorable conditions the corpuscular flow may be observed. Such capillaries are rare, however, on the general surface of the skin. In the skin overlying the matrix of the fingernail, many capillaries take such an horizontal course and in a single microscopic field a number of these vessels may be brought into focus at one time. Here one frequently sees a corpuscular flow without

FIG. 2.—A drawing of the finger tip to show the area of skin at the base of the finger nail which is used in the determination of the capillary blood pressure. The circle overlying this area represents the microscopic field when the skin is observed under a drop of oil with the aid of a strong light. The capillaries are slightly diagrammatic: A single focal plane will not bring them all into focus at one time.

offering any resistance to the blood stream. If a constricting pressure be applied to the upper arm the corpuscular stream due to slowing may be seen in many of the capillaries without difficulty. A drawing of the picture seen is given in Fig. 2. The sharply outlined capillaries are seen as red threads lying on a pink background. The picture is very much clarified if the skin be first scrubbed with soap and water and afterward thoroughly dried. This procedure removes the loose epidermis.

Capillary Observations. The application of this technique to this patient disclosed the following characteristics in the vessels. The subpapillary venous plexus was very prominent. There were many intervascular anastomoses and numerous capillaries were of the convoluted or cork-screw variety. The venous portions of the capillaries were especially dilated. In one capillary under observation the corpuscles altered their course taking first the normal then the reversed direction, that is, from the capillary back into the

arteriole. In the skin capillaries of man, unlike those of the frog's web, this is a pathologic phenomenon.

In a number of the other capillaries under observation there was a periodic acceleration and slowing of the blood stream. In fact there were phases when the *corpuscles coming from the arterial limbs of the capillaries collided with those regurgitated back from the venules to the capillaries.* The latter was obviously the result of venous stasis and regurgitation attending the tricuspid insufficiency. Such a *collision of corpuscles in the venous limbs of the capillaries is never seen in health.*

These clinical phenomena are almost a reproduction of those made by Cohnheim[4] on the capillaries of the frog's tongue after venous compression. The first effect noted by him was a periodicity in the bloodflow of the capillaries. Further venous obstruction caused a to-and-fro movement of the corpuscles without progress.

Our findings therefore prove the existence of back pressure in the venous system. *This single fact assumes great importance in the differentiation between circulatory failure due to back pressure, (venous stasis, right-sided cardiac failure) from that due to diminished vis-a-tergo, (left-sided cardiac failure).* In the latter case no such signs could be present. If both factors are present in a given case, the simple observation of the capillary flow in the human finger might be sufficient in order to evaluate the relative importance of each. In other words *capillary pulsation or better a sliding back and forth of the corpuscles without progress is direct evidence of venous back pressure. If the corpuscles from the arterial and venous limbs of the capillaries collide, it is probably pathognomonic of tricuspid regurgitation.*

The pressure in the capillaries was determined by the Danzer-Hooker method[3] with the microcapillary tonometer (Fig. 3). This instrument was placed on the microscopic stage and the finger on the rest, (3), under the chamber (A–B). The latter is absolutely transparent. Its roof consists of glass and the floor of peritoneal membrane or gold-beaters skin, which has been softened and cleared so that it is very pliable, adapting itself very readily to the skin. With a strong beam of light thrown down through the chamber, the capillaries were readily seen; and when air was pumped into the pressure capsule until the corpuscular flow slackened, certain striking phenomena became manifest. To understand them we must briefly refer to the normal phases of corpuscular movement occurring during capillary pressure determinations.

As the pressure acting upon the capillaries rises, the corpuscles begin to slow down their movement. As these structures are progressively compressed the stream becomes retarded to such a degree that the capillaries take on a beaded appearance. In other words, the corpuscles look like red marbles slowly rolling along the lumen of these vessels. We have termed this the "beaded flow." This is the first stage of capillary compression.

If the capillaries are further compressed the corpuscles begin to oscillate back and forth in the capillaries synchronously with each heart beat, but they make no progress. This is stage two of capillary compression.

When the pressure is raised 5 mm. more and the corpuscles cease to move altogether, stage three is reached, namely, that of corpuscular stagnation. The capillaries are now compressed to such a degree that the contractions of the heart have no influence on the circulation within them. Any further increment in pressure causes the corpuscles to leave the capillaries and enter the arterioles or the anastomosing capillaries of the deeper layers not affected by this compression. This is the last or fourth stage, that of corpuscular reversion.

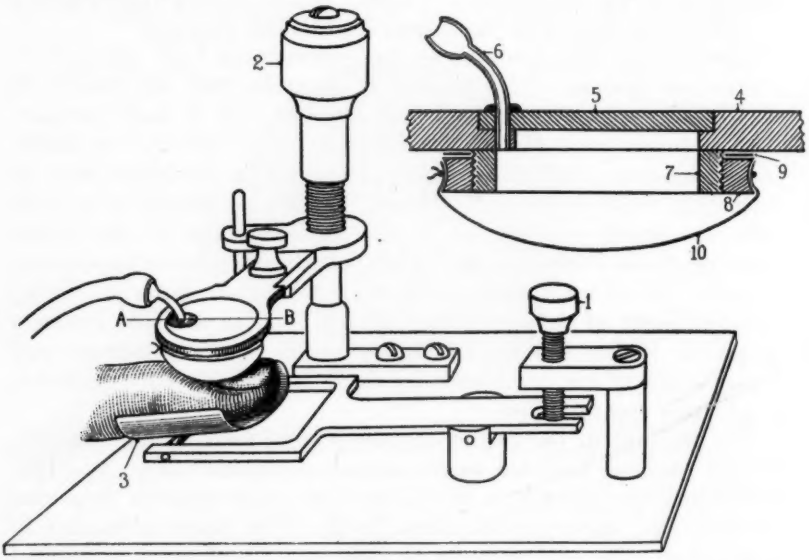

FIG. 3.—The microcapillary tonometer. The instrument is of such a size that it rests on the microscope stage. Description in text.

Our patient was suffering from heart failure associated probably with tricuspid insufficiency. When she was subjected to such studies, unusual reactions occurred. As the capillaries were compressed, the first stage or beaded flow was intermittent instead of continuous. A further increase of 5 to 6 mm. pressure caused not the usual stage two (corpuscular oscillation with no progress) followed by stage three (corpuscular stagnation). Instead reversion of the blood stream, namely, the last stage immediately followed the first one. In this case, however, the stage of corpuscular reversion instead of being a continuous one was intermittent. The latter was probably due to the systolic reflux of blood back into the veins brought about by the regurgitation through the dilated tricuspid ring.

Briefly stated, stage one was followed by the fourth stage. Both of these were intermittent instead of continuous. The periodicity of these two phases of corpuscular activity is the essential pathologic feature of our observations. The absence of stages two and three in themselves are not very unusual in certain capillaries even under normal conditions. The fact that the beaded flow and the corpuscular reversion stages were periodic is pathologic.

The oscillatory character of the corpuscular movements is accounted for by a retrograde capillary regurgitation or pulsation. Likewise the microscopic observations of the uncompressed capillaries showing alternately a slowing and acceleration of the blood stream, *the to-and-fro movement of corpuscles in one and the same capillary, and the phenomenon of corpuscular collision are likewise different manifestations of the retrograde capillary pulse.*

It is probable that the occurrence of a retrograde capillary pulse is sufficiently characteristic to be used diagnostically in obscure cases of tricuspid leakage, or to differentiate left from right sided heart failure, defective vis-a-tergo from venous back pressure.

Summary.—A retrograde capillary pulse was observed microscopically in a case of heart failure associated probably with tricuspid regurgitation. This was evident both on direct microscopic examination of the skin capillaries, as well as in the phenomena accompanying the determination of capillary blood pressure. The presence of a retrograde capillary pulse may be of value in the diagnosis of doubtful cases of tricuspid insufficiency or severe venous stasis.

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BLOOD SUGAR IN STATUS THYMICOLYMPHATICUS.

A New Theory as to the Cause of Sudden Death.

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In the majority of cases of status death that have come under observation in the wards of the Babies' Hospital the prostration of

the patient was so marked that it was out of all proportion to the general physical findings. The patients were well developed, and so well nourished that they were classified as fat babies. The physical examination showed only mild infection, as acute tonsillitis, or acute bronchitis, or small areas of bronchopneumonia. All the patients, however, were in a state of coma. There were convulsive movements, more or less generalized. The breathing was noisy and labored. The heart was rapid and its sounds were faint. There was a bluish-gray discoloration of the skin, and in some cases the patients were covered with perspiration. Since the clinical picture suggests a state of sugar shock from overdosage of insulin, it was decided to determine the blood-sugar level in these children. We are reporting our detailed findings in 3 cases:

Case Reports. CASE I.— *History.* V. O. B., a girl, aged twenty-four months, was admitted to the Babies' Hospital at 5 A.M. and died at 11.45 A.M. The family history was negative. The patient had had two convulsions at the age of eleven months. She was under observation in the Babies' Hospital at the age of eighteen months, with an attack of acute otitis media and acute tonsillitis. The day previous to this admission she had had three convulsions, lasting one and a half hours. At that time the blood calcium was 11.5 mg. and the phosphorus was 2.2 mg. per 100 cc. She was well until three days before the last admission. The illness began with drowsiness, which continued for two days. This was followed by severe abdominal pain. There was no fever. Severe generalized convulsions occurred at frequent intervals for six hours before death. During the convulsions chocolate-colored watery fluid came from the mouth.

Physical Examination. Physical examination revealed a white, well-developed fat child. She was in deep coma, from which she could not be aroused. The skin was bluish-gray in color. The convulsions involved the muscles of the face and extremities. The knee jerks were hyperactive. The liver and spleen were just palpable. There was a mild tonsillitis. The pulse was rapid and weak in volume.

Laboratory Findings. The spinal fluid was clear and under normal pressure. One cell was present. The Noguchi test for globulin was negative. The spinal-fluid sugar was 28 mg. per 100 cc. The chlorids were 650 mg. per 100 cc. The blood sugar was 52 mg. per 100 cc. The urea nitrogen was 20.8 mg. per 100 cc. The CO_2 combining power was 27 volumes per cent.

Necropsy. The body was that of a fat, well-formed, female, white child, with 0.5 cm. of panniculus adiposus over the abdomen and 1 cm. over the thorax. The neck was short. The skin and hair were fine in texture. The thymus was pink, moist and large. It weighed 18 gm., and covered the base of the heart. The

spleen weighed 28 gm. It was moderately increased in size; on section the Malpighian bodies were very prominent and numerous. The liver was fatty. In the intestines the solitary follicles were all enlarged, increasingly so toward the ileocecal valve. In the cecum the follicles were very large and numerous. The mesenteric lymph nodes were hyperplastic, pale and firm. The suprarenals were small, with a linear yellow cortex outlining a red medulla. The entire width was 2 mm. The weight of the suprarenals was 3 gm. The blood culture at autopsy gave no growth. Microscopic examination showed hyperplasia of the lymphoid cells in the spleen and solitary follicles of the intestines. Germ centers were present in most of the lymph follicles, which showed no evidence of necrosis. The suprarenals showed very slight degeneration of the cortical cells.

Anatomic Diagnosis. Status thymicolymphaticus. Fatty liver. Hypoplasia of suprarenals.

CASE II.—*History.* M. E., a boy, aged sixteen months, was admitted to the Babies' Hospital at 3.30 P.M. and died at 7.45 P.M. The father and mother were in good health. Three months ago the patient had pneumonia with otitis media. The present illness began with a cough, of one week's duration. Fever began on the night before admission. Moderate vomiting continued all day. Dyspnea and cold perspiration were present for about ten hours previous to death.

Physical Examination. Physical examination showed a very well-nourished, well-developed, white, male infant. He was in a state of coma, and gave no response to stimulation. The respirations were noisy and labored. The skin was covered with cold perspiration. There was slight cyanosis. This condition persisted until two hours before death. The patient then went into a generalized convulsion, which lasted until death. There was an acute tonsillitis and pharyngitis. At the right apex there was a small area of bronchopneumonia. The liver and spleen were both slightly enlarged. The knee jerks were hyperactive.

Laboratory Findings. Lumbar and cistern punctures were performed. The fluid in both cases was clear and under slightly increased pressure. There were 6 cells in the spinal fluid and 8 cells in that taken from the cistern. A faint trace of globulin was present in both. The blood sugar was 42 mg. per 100 cc. and the chlorids were 550 mg. per 100 cc. The spinal-fluid sugar was 62 mg. per 100 cc. and the chlorids 738 mg. The cistern-fluid sugar was 64 mg. per 100 cc. and the chlorids 725 mg. The blood and spinal-fluid cultures remained sterile after four days' observation.

Necropsy. The body was that of a well-nourished, male, white infant. There were small scattered areas of bronchopneumonia in both lungs. The heart was normal. The thymus weighed 34 gm.

It was pink and normal in consistency. The spleen weighed 60 gm. It was much enlarged, firm and congested. The Malpighian bodies were distinct. A supernumerary spleen measuring 1.5 cm. was present. The liver was moderately fatty. Throughout the small intestines the solitary follicles and the Peyer's patches were greatly enlarged. In the colon the solitary follicles were also large. The suprarenals were normal.

Anatomic Diagnosis. Status thymicolymphaticus. Hyperplasia of thymus, spleen and intestinal and mesenteric lymph nodes. Bronchopneumonia. Fatty liver.

CASE III.—*History.* T. L., a boy, aged twenty-two months, was admitted to the Babies' Hospital, at 2.30 P.M. and died at 10 P.M. The family history was negative, except for the death of one infant, two days after a normal delivery. The patient had whooping cough at fourteen months and measles at eighteen months. The present illness began with slight jaundice, three days before admission. Vomiting and fever were marked symptoms in the forty-eight hours previous to death. The infant was drowsy on the day of admission.

Physical Examination. Physical examination showed a very well-developed and well-nourished, white, male child. The skin was moist, with a slightly icteric tint. The mucous membranes were jaundiced. He was in a state of coma. The respirations were labored. The pulse was weak. Just before death there was a slight, generalized twitching of the muscles. There were moist rales over both lungs. The liver was moderately enlarged and rather firm. The spleen was just palpable. The knee jerks were hyperactive.

The patient was transfused, receiving 110 cc. of blood from the father, by the direct method.

Laboratory Findings. Blood count before transfusion: Red blood cells, 1,500,000; hemoglobin, 25 per cent; white blood cells, 40,600; polymorphonuclears, 61 per cent; lymphocytes, 30 per cent; mononuclears, 7; transitionals, 3; nucleated red cells, 45 per 100 white cells counted; blood platelets, 336,000; anisocytosis, poikilocytosis and achromasia. The urine after transfusion was bloody, and contained protein (4+ in amount). The guaiac test was markedly positive. There were no red blood cells or casts noted on microscopic examination. The spinal fluid was clear and under normal pressure. There were 4 cells. The Noguchi test for globulin was faintly positive. The blood culture showed no growth after four days of observation. The blood sugar was 57 mg., and the chlorids 600 mg. per 100 cc. The spinal-fluid sugar was 26 mg. and the chlorids 775 mg. per 100 cc.

Necropsy. This was a well-nourished, white, male child, mildly jaundiced. The necropsy was performed at the city morgue, by the medical examiner, to whose courtesy we are indebted for speci-

mens from the thymus, spleen and intestines. There was a large amount of subcutaneous fat. The heart was normal in size. Pulmonary edema and a fatty, congested liver were found. The thymus gland weighed 39 gm. It was very much enlarged, but of normal consistency. The spleen was enlarged, and the Malpighian bodies were prominent. Throughout the intestines the solitary follicles were enlarged. The suprarenals were normal.

Microscopic Examination. Microscopic examination showed hyperplasia of the Malpighian bodies in the spleen, lymphoid tissue of the solitary follicles of the intestines and the thymus.

Anatomic Diagnosis. Status thymicolymphaticus. Fatty, congested liver.

In these 3 cases of status thymicolymphaticus with convulsions, in which the blood sugars were estimated immediately before death, we found sugar values of 42, 57 and 52 mg. per 100 cc. (Table I). The figures are considerably below normal. We have found the normal blood sugars for infants, as determined by the Myers-Bailey modification of the Lewis Benedict method, to be between 80 and 120 mg. per 100 cc. The sugar of normal spinal fluid, estimated by the same technique, varies between 45 and 65 mg. per 100 cc. In 2 of these children the amount of sugar in the spinal fluid was less than normal, 26 and 28 mg. per 100 cc. In the third instance the sugar in the spinal fluid was 62 mg., in the cistern fluid 64 mg. and in the blood 42 mg. per 100 cc. However, in this case pneumonia was present. In a certain percentage of our pneumonia cases, in which we have examined the spinal fluid, we have found the sugar increased in amount with a consequent disturbance of the spinal-fluid sugar to blood-sugar ratio. The spinal-fluid sugar may at times be 100 per cent or more of the blood sugar, as compared with the normal 50 to 60 per cent. A parallel decrease in the blood and spinal-fluid sugar in such a case might give a spinal-fluid sugar which is higher than the blood sugar.

The blood sugar was determined within half an hour before death in a series of patients with diseases other than status thymicolymphaticus. The values were all normal or above normal. Hypoglycemia is therefore not a constant finding before death. (Table II).

The 3 patients had severe generalized twitchings for two to six hours previous to the time the blood sugar was estimated. It was just possible that the exercise involved might have been sufficient to deplete the glycogen reserve of the body and result in hypoglycemia. We have, there, estimated the blood sugar in convulsions produced by other conditions than status thymicolymphaticus. As shown in Table III, the blood sugar in such instances came within the upper range of normal, or was slightly above normal. It does not seem probable, therefore, that the convulsions alone produced the low blood sugar.

TABLE I.—BLOOD CHEMISTRY OF PATIENTS WITH STATUS THYMICOLYMPHATICUS WHILE IN CONVULSIONS.

Case.	Initials.	Age, months.	Sex.	Time in convulsion before taking blood.	Blood chemistry in mg. per 100 cc.				Spinal fluid in mg. per 100 cc.		Cistern fluid in mg. per 100 cc.	
					Sugar.	Chlorids.	Urea Nitr.	CO_2 c. p.	Sugar.	Chlorids.	Sugar.	Chlorids.
I . . .	V. O. B.	24	F.	5½ hrs.	52	. . .	20.8	27 vols. per cent	28	650		
II . . .	M. E.	16	M.	2 hrs.	42	550	. . .	. . .	62	738	64	725
III . . .	T. L.	22	M.	12 hrs.	57	600	. . .	. . .	26	775		

TABLE II.—BLOOD SUGARS DONE WITHIN HALF AN HOUR OF DEATH IN PATIENTS SUFFERING FROM DISEASES OTHER THAN STATUS THYMICOLYMPHATICUS.

Case.	Age.	Sex.	Diagnosis.	Blood sugar, mg. per 100 cc.	Spinal-fluid sugar, mg. per 100 cc.	Remarks.
I	2 yrs.	M.	Anemia; lead poisoning	188	94	Autopsy performed by medical examiner. Only cause of death anemia. Suprarenal normal. Spleen negative. Thymus 15 gm. Lymph nodes normal. Convulsions for three hours before death.
II	5½ yrs.	F.	Acute intestinal intoxication	202	. .	Twitching of muscles of extremities. In state of coma.
III	8 mos.	M.	Tuberculosis of cerebral and spinal meninges	141	12	
IV	10 mos.	M.	Acute intestinal intoxication; Mongolian idiocy	101	. .	
V	9 mos.	F.	Acute nephritis; bronchopneumonia; acute catarrhal colitis	93	. .	
VI	3 yrs.	F.	Tuberculosis of cerebral and spinal meninges	165	28	

TABLE III.—BLOOD CHEMISTRY OF PATIENTS IN CONVULSIONS PRODUCED BY OTHER CONDITIONS THAN STATUS THYMICOLYMPHATICUS.

Case.	Age.	Diagnosis.	Time in convulsion before taking blood.	Blood chemistry, in mg. per 100 cc.				Spinal fluid.		Result.	Necropsy.
				Sugar.	Chlorid.	Ca.	P.	Sugar.	Chlorid.		
I . . .	8 mos.	Broncho-pneumonia	8 hrs.	140	650	10.5	3.5	130	675	Died	Thymus, 5 gm.; spleen negative; suprarenal normal
II . . .	6 mos.	Tetany	6 hrs.	106	...	7.7	4.0	...	...	Improved	
III . . .	12 mos.	Tetany	24 hrs.	130	500	...	...	86	673	Died	Thymus, 5 gm; Spleen negative; suprarenal normal.
IV . . .	5 mos.	Tetany	4 days, 2 to 3 per hour	106	...	5.2	5.3	71	763	Not improved	
V . . .	....	Streptococcus meningitis	3 hrs.	134	...	...	...	19	500	Died	
VI . . .	2 yrs.	Anemia, lead poisoning	3 hrs.	188	538	...	...	94	675	Died	Autopsy performed by the medical examiner who gave the only cause of death as: anemia; suprarenal, normal; spleen, negative; thymus, 15 gm; lymph nodes, normal

We have estimated the blood sugar in a series of patients with status thymicolymphaticus, as evidenced by roentgenograms which showed thymic enlargement (Table IV). The patients were not

TABLE IV.—BLOOD SUGAR OF PATIENTS WITH STATUS THYMICOLYMPHATICUS WHEN THEY WERE NOT IN CONVULSIONS.

Case.	Age (months).	Sex.	Diagnosis.	Blood sugar, mg. per 100 cc.	Remarks.
I . . .	21	F.	Hypertrophied tonsils; hyperplasia of thymus	106	No history of convulsions
II . . .	3½	F.	Enlarged adenoids; hyperplasia of thymus	72	History of convulsions
III . . .	4	M.	Status lymphaticus; rickets	111	No history of convulsions
IV . . .	6½	M.	Hyperplasia of thymus; acute intestinal intoxication	86	No history of convulsions
V . . .	13	M.	Hyperplasia of thymus; acute tonsillitis	89	No history of convulsions
VI . . .	4	M.	Enlarged thymus	103	Difficulty in breathing

in convulsions at the time the blood was taken, and the blood-sugar values were within the normal limits, with exception of one which was slightly decreased. The hypoglycemia, therefore, was temporary rather than continuous.

We were particularly interested in this hypoglycemia because it appeared to throw new light on the cause of sudden death in status thymicolymphaticus, for which many explanations have been advanced. Kopp[2] is responsible for the idea that mechanical pressure of the enlarged thymus on the trachea causes death. Wooley[3] and others attributed it to overfunction of the thymus. Timme[4] thought death followed adrenal exhaustion and hemorrhage from the thin vessels into the adrenals or ventricles of the brain. There is still another theory that death is the end result of intoxication from products of faulty metabolism. Blumer[5] held that a substance, probably a nucleoprotein, released from the necrosed germinal follicles, was immediately responsible. Symmers[6] has sponsored the theory that death is due to an anaphylactic reaction. We, however, feel that acute suprarenal insufficiency is the immediate cause of death.

It is known that a low blood sugar may be due to suprarenal insufficiency. Porges,[7] Bierry and Malloizel,[8] and Mayer[9] have reported low blood sugar in animals after extirpation of the suprarenals. Griffith[10] found in cats in which suprarenals were immobilized (one taken out and one denervated) a lower and more stable blood sugar than in his control cats. In Addison's disease, in which

the suprarenals are degenerated, a low blood sugar is found.[11] Moreover, recent work done by Cannon, McIver and Bliss[12] has shown that the sympathetic adrenal mechanism is a protection to the body against the dangers of a hypoglycemia. The critical point seems to be between 70 and 80 mg. per 100 cc. Reductions below the limit call into action a sympathetic adrenal factor, working to prevent further reduction (Cannon[13]).

The suprarenals are frequently hypoplastic in status thymicolymphaticus. In 1905 Norris[14] first called attention to the frequent association of status thymicolymphaticus with Addison's disease. Later Norris and Wiesel[15] showed hypoplasia of the suprarenals to be of almost constant occurrence in status thymicolymphaticus.

The association of thymic enlargement with diseased suprarenal has been definitely established by the work of Wiesel,[16] Hedinger,[17] Hart[18] and Pappenheimer.[19] Moreover, an anatomic condition similar to status thymicolymphaticus has been produced in experimental animals, following suprarenalectomy (Crowe and Wislocki,[20] Marine, Manley and Bauman,[21] and Jaffe[22]).

A slight shock, anesthesia, emotional excitement, or a mild infection, is very often the only discernible cause of the status death. Circumstances such as these call forth a hyperglycemia in the normal person. According to Cannon,[23] the suprarenals are instrumental in this sugar mobilization. Griffith[10] has shown that there is much less augmentation of the blood sugar by mild stimuli in cats, in which the suprarenals have been immobilized, when there is no possibility of reinforcement by the suprarenals, than is the case in normal cats. If, as the figures in our 3 cases would seem to suggest, patients with status thymicolymphaticus develop a hypoglycemia instead of a hyperglycemia, which is the normal response of the organism to like conditions, it is a fact of some import. It suggests failure on the part of the hypoplastic suprarenals to carry on their normal function of sustaining the body in time of stress. It is an indication of acute suprarenal insufficiency at the moment of status death.

Acute suprarenal insufficiency may cause sudden collapse, asthenia or death (Lavenson[24]). This is seen in death due to suprarenal hemorrhage in the newborn. Rabinowitz[25] has reported 2 deaths in cases of suprarenal hemorrhage. A similar case has been observed in the wards of the Babies' Hospital:

CASE IV.—*History.* The patient, a white female, aged ten months, was admitted to the Babies' Hospital four days before death. She had been jaundiced since she was two weeks old. Diarrhea had been present for two weeks, and anorexia for three days before admission. She was poorly nourished and developed. There was an extremely offensive odor to the breath. The skin was dry and jaundiced. The spleen and liver were enlarged and

extended 2 inches below the costal margin. Two days after admission subcutaneous hemorrhages were noticed on the back and abdomen. On the following day the baby developed convulsions which terminated in sudden collapse. The extremities were spastic until death fourteen hours after. A chemical examination of the blood was made two hours before death. Blood sugar was 25 mg., urea nitrogen 18.5 mg. and uric acid 3.1 mg. per 100 cc., and icteric index 115. The autopsy showed general icterus, cirrhosis of the liver, atresia of the hepatic duct, chronic perisplenitis, chronic nephritis and suprarenal hemorrhage. The subcutaneous hemorrhages, the sudden collapse, the onset of convulsions, with the low blood sugar, suggested suprarenal hemorrhage, which was confirmed by autopsy.

The evidence cited warrants the assumption that the hypoglycemia is an indication of suprarenal insufficiency. There is, also, experimental proof for the statement that the acute suprarenal insufficiency causes death. Therefore, if the hypoglycemia should prove to be a constant finding it suggests an acute suprarenal insufficiency, which simply and adequately explains the sudden death in status thymicolymphaticus. We realize the paucity in the number of patients, but as in the eighteen months since this work was begun we have been able to study the blood sugars in but 3 cases, we felt that by publishing these the necessary data, in corroboration or disproof, would be obtained more readily.

Summary. 1. In 3 cases of status thymicolymphaticus we have found the blood-sugar values to be low (42, 52, 57 mg. per 100 cc.).

2. In 1 case of suprarenal hemorrhage a blood sugar of 25 mg. per 100 cc. was found.

3. In 6 cases of convulsions produced by conditions other than status thymicolymphaticus we found the blood sugars normal or increased above normal.

4. In 6 cases of enlarged thymus shown by roentgenograms we found 5 blood sugars within normal limits and 1 very slightly decreased.

5. In 6 cases where the blood sugar was determined within half an hour before death on patients with diseases other than status thymicolymphaticus, the values were normal or above normal.

6. Acute suprarenal insufficiency is suggested as the immediate cause of sudden death in status thymicolymphaticus.

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FAMILIAL MEDIASTINAL LYMPHOGRANULOMA.

Report of Three Cases in one Family.

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(From the First Medical Clinic, University of Vienna, Prof. K. F. Wenckebach. I wish to thank Dozent Dr. Karl Hitzenberger, roentgenologist of the clinic, for the opportunity of studying the cases here reported.)

Hodgkin's disease is considered to be a specific infectious granuloma of unknown cause, always affecting the lymphatic apparatus of the body, and leading to a progressive and finally almost universal swelling of the lymph glands, with secondary involvement of the various organs and death. The first sign of the disease is usually enlargement of the lymph nodes in a localized area. It may be primary: (1) In the cervical glands; (2) axillary glands; (3) inguinal glands; (4) retroperitoneal glands; (5) mediastinum; (6) mesenteric glands; (7) spleen; (8) gastrointestinal tract; (9) lungs. In addition to the enlargement of the lymph nodes with the characteristic histologic changes, first described by Sternberg and Paltauf, the chief symptoms are the following: Recurring attacks of fever, a chronic relapsing fever; an unspecific blood picture with a polymorphonuclear neutrophile leukocytosis, and sometimes eosinophilia and a relative or absolute reduction of the lymphocytes; pruritus, which is a common early symptom and often leads the patient to a dermatologist; a brownish diffuse or spotted pigmentation on the face and trunk; marked sweating; toxic symptoms such as loss of weight, poor appetite, emaciation and diarrhea in the

advanced stage of the disease; enlargement of the liver and spleen with amyloid changes in some cases.

The exciting cause of lymphogranuloma has been sought by many investigators but no microörganism has as yet been found with which Koch's postulates can be fulfilled for this disease. The tubercle bacillus, corynebacterium granulomatis maligni, spirochetes, protozoa, streptococci, and others have been found in the lymph nodes. None of these has produced the disease in experimental animals.

I have had the opportunity of studying a large number of cases of lymphogranuloma clinically and pathologically in the past three years and have found that the disease can affect almost every organ in the body, but I shall discuss the pathology of the disease in another publication. Here I wish to summarize our present knowledge of the predisposing causes of Hodgkin's disease and to call attention to certain facts which may aid us in the further elucidation of the nature of this fatal disease which seems to have increased considerably in most civilized countries in the past ten years. I wish also to report 3 cases of mediastinal lymphogranuloma in one family, and to discuss the mediastinal form of Hodgkin's disease.

Predisposing Causes. *Age.* Although Hodgkin's disease has been seen at all ages, it is very rare in the first year of life. No case of congenital disease has been demonstrated. The youngest known case is that of an infant aged five and a half months. The oldest reported case is a patient aged seventy-six years. It is most common at the ages of twenty to forty years. About 30 per cent of the cases occur in the first two decades, 50 per cent in the third and fourth, and the remaining 20 per cent after the fortieth year of life.

Sex. All the statistics of large numbers of cases of Hodgkin's disease indicate a greater prevalence in males than in females. Ziegler's summary of 220 cases shows a ratio of about 2 to 1. Fabian with 184 cases found a ratio of 3.5 to 1, and Desjardins and Ford with 145 cases, 2.3 to 1. Lubarsch reported 9 cases between 1911 and 1914, 6 males and 3 females, and from 1915 to 1918, 28 cases of which 26 were males and only 2 females. The frequency of the disease in males at the most active period of life might suggest a relationship to certain occupations but this has not been demonstrated.

Constitution. According to Ziegler a special body constitution plays no role in the development of Hodgkin's disease. Usually strong, previously entirely well persons are attacked. However, it is possible that lymphogranuloma may require a special constitutional terrain for its development (J. Bauer), and that this may be true of other lymph gland diseases, such as lymphosarcoma (which is also more common in males than in females).

Status Lymphaticus. Perhaps a condition of status lymphaticus makes the individual more susceptible to Hodgkin's disease. Stoerk

found in the cases of lymphogranuloma described by him almost always the lymphatic type of individual. Glanzmann has recently called attention to the close relationship of granulomas, sarcoid tumors and simple hyperplasia of the lymph nodes. Bauer mentions a case of lymphogranuloma with three types of lymphatic disease found at the autopsy—typical lymphogranuloma, tuberculosis and lymphosarcoma. A status lymphaticus may offer more favorable conditions in the tonsils, intestinal mucosa, and the respiratory tract for the invasion of bacteria, besides lowering the general resistance. Individuals with status lymphaticus or thymico-lymphaticus seem to be especially endangered by infectious diseases. This "locus minoris resistentiæ" in the lymphatic tissues may be transmitted as a defect in structure or function. We know that in certain families the chief diseases to which liability exists are located in the mucous membranes of nose, throat, and bronchi (Davenport). In another family the weakness may be in the lungs, ears, skin, kidney, or lymphatic apparatus (Rosenau).

It is possible that individuals with status lymphaticus may be more susceptible to generalized Hodgkin's disease, and that those with status thymicus may be predisposed to the mediastinal form. Barock, Ducrot and Hedinger have called attention to the familial occurrence of cases of status thymicus. In such cases the entire lymphatic apparatus need not always be hyperplastic. In fact, when the hyperplasia of the lymphatic apparatus coexists, then the thymus enlargement is usually not so marked. It is possible that the 3 cases of mediastinal lymphogranuloma, all in males of the same family, which I wish to describe in this publication are the result of a familial predisposition to Hodgkin's disease produced by a status thymicus. We shall discuss this matter later.

Occupation. People of most varied occupations are affected. No occupation has been found to predispose to the disease. It is seen under the best as well as the poorest hygienic conditions, in city as well as in the country, among the rich as well as the poor. Stengel claims that the poor are more often affected and he attributes this to chronic alcoholism. Gulland also believes that bad living conditions increase the chances of attack with this disease. Others take the opposite view and look upon it as a disease of the well-to-do (Fabian).

Other Diseases. Various disease conditions have been mentioned as predisposing causes. Trousseau mentions otitis media, with subsequent glandular enlargement, also infections of the upper respiratory tract. Cornil, Schulz and Fischer see a relationship to scrofulous changes, rickets and other nutritional disturbances. All of these seem to be wanting in the majority of cases. A number of authors look upon tuberculosis as a predisposing cause. But Ziegler finds no evidence for this. Of 54 cases studied by him he could find no evidence of tuberculosis in the family in 45. Perhaps

certain diseases which lead to chronic lymph gland changes may render individuals more susceptible. In 2 of the 3 cases which I shall report repeated attacks of tonsillitis and pharyngitis were present in the case history, in the third no accurate history was available. Desjardins and Ford also state that they have been impressed by the frequency with which the disease has been found in relation to common chronic lesions of the mouth and nose.

Heredity. In the literature are found only a few reports of lymphogranuloma in more than one member of a family. Ziegler stated in 1911 that there were no recorded cases of the disease in parent and child and that no hereditary predisposition had been demonstrated. Peacock and Senator have reported cases in twins, Degen saw a brother and sister with the disease. Braun, in 1912, reported 3 cases of malignant disease of lymph glands in a woman and her two brothers. Within a period of six years one developed a sarcoma of the mediastinum, another a malignant lymphoma of the mesentery, and a third a "pseudo-leukemia" which developed into a leukemia. The three people had lived apart for years. I wish to report 3 cases of mediastinal lymphogranuloma in one family, all men, and to discuss the clinical symptomatology of this form of the disease.

Mediastinal Lymphogranuloma. Just as Hodgkin's disease may localize at first in the neck glands, axilla, or abdominal lymph nodes, so also may it produce solitary tumors in the anterior mediastinum. It seems that the loose connective tissue of the mediastinum furnishes a favorable site for the development of the granuloma. Some authors (Ziegler) believe that in children the thymus gland is the seat of the change. I am of the opinion that in adults a persistent thymus, largely a lymphoid organ, may make a predilection in the anterior mediastinum toward lymphogranuloma. If such a solitary mass originates in the thymus it is easy to understand how large tumor masses spread into the surrounding loose areolar tissue and along the peritracheal and peribronchial lymphatics. There is very little resistance to the growth in the anterior mediastinum. The loose fat tissue formerly occupied by the thymus may, by its peculiar structure, promote the spread of the granuloma, and lend to it the characteristic lobular appearance (see Roentgen ray photograph of Case III before treatment). I have also observed in a number of cases that the mediastinal masses disappeared more rapidly under Roentgen ray treatment than do the enlarged lymph nodes in the neck or axilla. In fact, the masses may entirely disappear so that the patient later presents the picture of a localized or generalized lymph-gland involvement although the process was primary in the mediastinum. In the later progress of the disease the mediastinal masses may be absent with spread of the disease to the lungs, pleura, pericardium, liver, spleen, bone marrow, and so forth.

The question whether lymphogranuloma can be primary in the anterior mediastinum is answered differently by different writers. That the disease may first manifest itself in the mediastinum is accepted by most. Solitary mediastinal tumors undoubtedly occur, but are exceptional just as are localized axillary, inguinal or retroperitoneal granulomas. They are usually secondary to enlargement of the glands of the neck, or the peritracheal glands. In most cases of mediastinal Hodgkin's disease the patient consults the physician when there are also malignant lymphomas of the cervical, axillary, inguinal or retroperitoneal glands. In such cases it is not possible to say which is primary or which secondary. A mediastinal tumor may remain dormant for some time and only be recognized when it has spread into the neighboring structures or produced marked pressure symptoms. Hence the size of the tumor tells us little as to its age.

According to Ewing, those cases of Hodgkin's disease in which the mediastinal tumor forms the chief lesion arise from the thymus. He states that their structure is usually typical of granulomatous or sarcomatoid processes of thymic tissue. He further says that a large proportion of the lymphogranulomas which terminate in sarcoma in the mediastinum find their origin in the thymus. These Hodgkin's sarcomas are not true sarcomas; they differ in cell type and origin, and have less invasive power than the lymphosarcoma. Some authors (Ewing, Yamasaki, Karsner, Welch) look upon Hodgkin's sarcoma as an example of a transformation of an infectious granuloma into a neoplasm. Kaufmann, however, states that it is not necessary to assume a sarcomatous change in these granulomas because they possess an infiltrative and destructive growth. They resemble sarcoma in their aggressiveness but that alone does not justify the use of the term sarcoma.

The symptoms of mediastinal Hodgkin's disease are chiefly due to pressure. The usual roentgenologic picture is that of a large lobulated tumor which enlarges the mediastinal shadow to the right and to the left. It usually has a curved, wavelike outline (see Roentgen ray photograph, Case III). In the upper sternum region there is an area of dullness, often reaching to the cardiac dullness. The lung borders are in the upper portions often pushed aside, and not infrequently the area of dullness combines with supraclavicular granulomata on both sides. The lung apices may be compressed. In advanced cases evidence of bronchostenosis appears. The trachea itself may be compressed or even invaded by the lymphogranuloma. I have seen in a number of cases of mediastinal lymphogranuloma sharply circumscribed round or oval shadows in the lung fields indicating lung metastases. In fact, one case which I saw was diagnosed during life as tumor metastases and proved to be a case of pulmonary lymphogranuloma.

There may be a localized edema over the sternum. The inter-

costal veins may be dilated in the upper part of the thorax. Rarely symptoms due to compression of the vena anonyma or of the vena subclavia appear, with venectasies of the arm and axilla. Or, the vena cava superior may be compressed, with passive congestion of the upper part of the body and head. Anastomoses between the two vena cavas become visible. Marked cyanosis, edema of the arms and chest, and in women enlargement of the breasts, occur in the late stage.

Irritation or paralysis of the sympathicus, and vagus irritation may cause cardiac disturbances such as tachycardia, or attacks of dyspnea. Recurrens paralysis has been seen. The trachea may be dislocated as well as compressed, and glottis edema may endanger the life of the patient. Death usually results from respiratory and circulatory disturbances. Pleural effusions occur in cases with extension to the parenchyma of the lung or the pleura itself. There may be involvement of the pericardium with the symptoms of a pericarditis. I have seen one case with extension to the myocardium. Esophageal compression or even perforation of the esophagus may develop.

In the mediastinal tumors which are a part of a generalized lymphogranulomatosis, the pressure symptoms are usually not so marked; the disease progresses without interruption, involving the abdominal glands and organs and then goes over into a cachectic state. In the mediastinal type one has the impression that the spread of the process toward the abdomen meets with a certain resistance or barrier, at least for a considerable length of time.

Case Reports. I wish to present the findings in 3 cases of mediastinal Hodgkin's disease occurring in one family, which were studied at the Wenckebach Clinic, University of Vienna.

Family History. M. S. (Case I) was born in 1865, married and had two children, a son (Case III) now twenty-seven years of age, and a daughter now twenty-five years of age. His wife is forty-seven years of age and apparently well. M. S. had three brothers and two sisters. Two of the brothers were killed in a railroad accident, one at the age of thirty years, the other at forty years. The third brother is fifty-seven years of age and well. The two sisters are well. The brother who was killed at forty had three children, a daughter now twenty-eight years of age, married and well, and a son (Case II) who died at the age of twenty-three years of mediastinal lymphogranuloma, and a second son thirty-three years of age and well.

M. S. died in 1899, at the age of thirty-four years, of "mediastinal tumor." At the time of his death his son (Case III) was only one and a half years of age, and his nephew (Case II) only two years of age. Twenty-one years after the death of M. S., his nephew came to the Wenckebach Clinic with mediastinal lymphogranuloma. His son (Case III) has developed the disease twenty-four years

FIG. 1.—Case III. Mediastinal lymphogranuloma. Roentgen ray photograph of chest on July 2, 1923, when the patient came to the clinic.

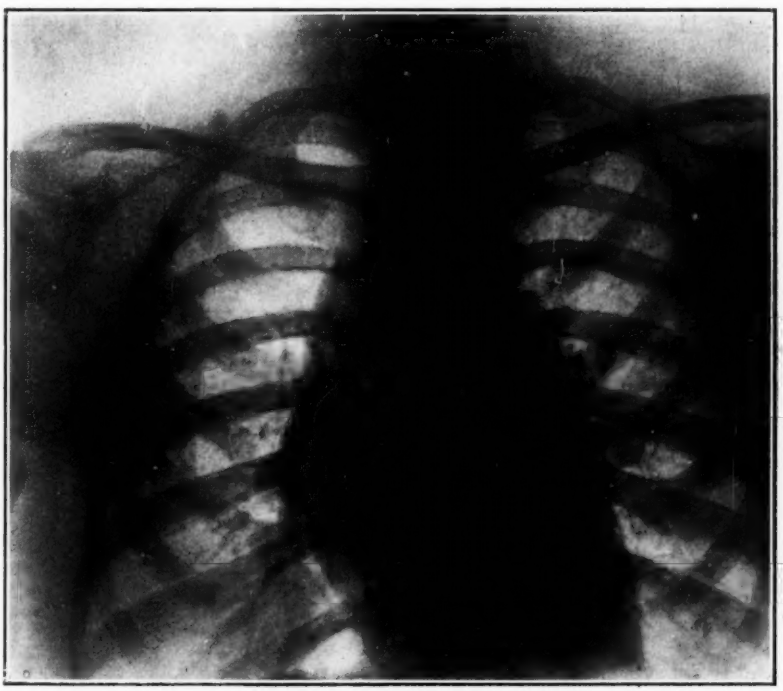

FIG. 2.—Case III. Mediastinal lymphogranuloma. Roentgen ray photograph of chest on September 26, 1923, after six Roentgen ray treatments at the clinic. The tumor is greatly reduced in size.

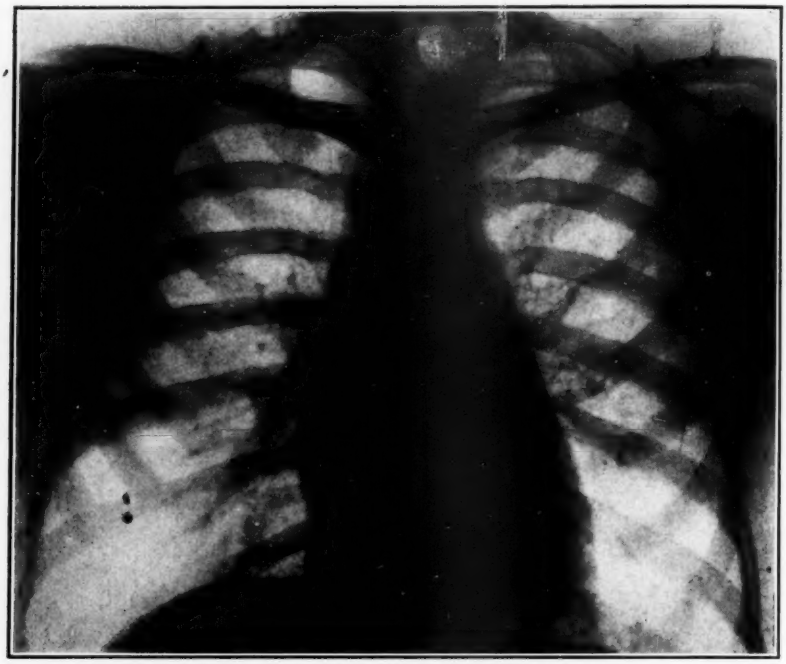

FIG. 3.—Case III. Mediastinal lymphogranu'oma. Roentgen ray photograph of chest on December 5, 1923, after second series of Roentgen ray treatments at the clinic. The mediastinal tumor has almost disappeared.

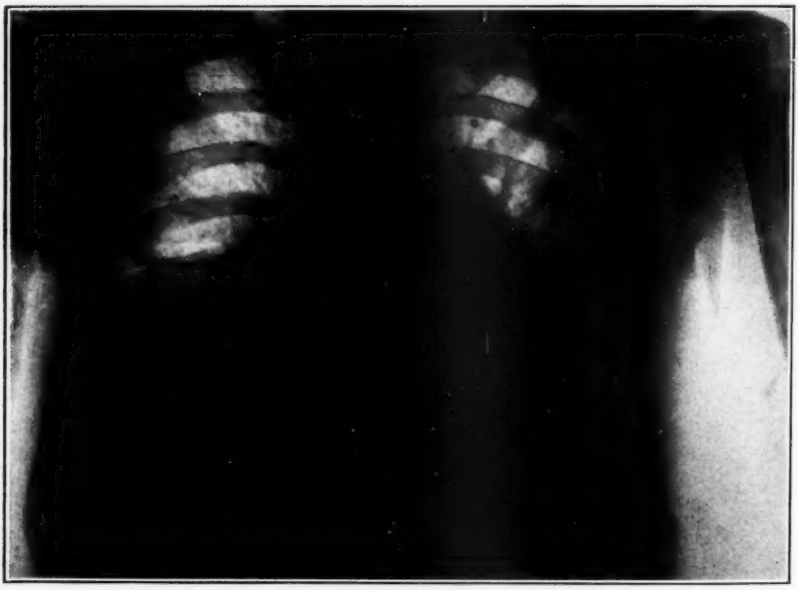

FIG. 4.—Case III. Mediastinal lymphogranuloma. Roentgen ray photograph of chest on November 27, 1925. A diagnosis of bilateral pleural effusion with pericarditis and possible involvement of the myocardium was made. The autopsy on December 22, 1925, confirmed the diagnosis, showing a lymphogranuloma of the thymus region with extension to the pleura, pericardium and myocardium. (See autopsy report.)

after his death, and is now under treatment for mediastinal Hodgkin's disease. There is no history of tuberculosis in the parents of M. S. On the other hand, his wife's brother died of tuberculosis and three of her sisters died at birth or shortly thereafter, cause unknown. She has one brother who is forty-seven years of age and well.

Summarizing the family history, we are dealing here with 2 cases of mediastinal Hodgkin's disease and 1 case diagnosed twenty-four years ago as mediastinal tumor. The first case died in 1899 at the age of thirty-four years; the second, a nephew (brother's son) died twenty-one years later of mediastinal lymphogranuloma at the age of twenty-three years; and the third patient, a son, has mediastinal lymphogranuloma (twenty-four years after his father's death) at the age of twenty-seven years.

CASE I.—Mr. M. S., who had always been well, consulted his family physician in 1899, at the age of thirty-four years, complaining of a feeling of pressure in the chest, chiefly behind the sternum, and between the shoulder blades. This was accompanied by a choking sensation at times and some shortness of breath. The trouble had developed gradually over a period of several months. The physician who examined him made the diagnosis of mediastinal tumor, at a time when the disease lymphogranuloma had not yet been clearly established as a clinical entity. The physician who attended him has informed me that the condition resembled that of a mediastinal lymphogranuloma, as the patient developed enlargement of the cervical and axillary glands, which at first were soft and discrete and later became harder and always movable beneath the skin. The dyspnea increased, and was accompanied by cyanosis of the face and swelling of the neck. He also developed edema of the upper part of the chest, neck and face. The patient was confined to bed during the last two months of his illness because of severe dyspnea and pain in the chest. The patient died (six months after first consulting his physician) of respiratory failure.

Summary of Case I. Although we have no Roentgen ray or other laboratory findings yet the course of the disease as described by his own physician is such as we see in mediastinal lymphogranuloma. How long the patient had his mediastinal tumor it is impossible to state. After a duration of about a year the patient died of respiratory failure. Twenty-four years ago lymphogranuloma could not be diagnosed as today, with our Roentgen ray and laboratory aids.

CASE II.—Mr. P. S. was born in Vienna and lived there all his life. At the time of his admission to the hospital in 1917 he was a medical student, twenty years of age.

Past Illnesses. The patient stated that he had frequent attacks of sore throat, and tonsillar abscess, during childhood. He had measles at twelve years of age, followed by bronchopneumonia. Otherwise he was always well. In August, 1917, the patient entered the hospital with a severe bronchitis, fever and chills. He had some symptoms of a heart neurosis and frequent attacks of insomnia. He also had psoriasis for which he was receiving treatment. In September he developed a severe sore throat with an eruption over the entire body, followed by desquamation (scarlet fever?). After six weeks he had another attack of angina with some desquamation of the skin. Then followed periods of fever with the temperature as high as 40° C. He had attacks of palpitation of the heart, and dyspnea on walking or climbing steps. He also complained of pain in the spleen region. On November 16, the patient appeared very pale, the face somewhat edematous, also the legs. The pharynx was reddened and the tonsils enlarged. The heart dullness was increased to the right as well as to the left, and there was a systolic murmur at the apex. The abdomen was negative, the spleen not palpable. On February 28, the lymph glands on the right side of the neck were enlarged, the left inguinal glands also. On March 29, 1918, the spleen was palpable, the temperature rose to 40° C. There were pains in the joints. On April 18, the leukocytes were 15,200 with 85 per cent neutrophiles. On May 17, the patient was transferrred to the Wenckebach Clinic with the probable diagnosis of endocarditis and enlarged lymph glands. On May 22, a fluoroscopic examination revealed a large mediastinal tumor extending into the right and the left hilus regions. May 24, a blood examination showed: Red blood cells, 5,400,000; leukocytes, 18,500. The urine was negative. The patient left the hospital June 6, 1918. On April 27, 1920 (almost two years later), the patient entered the hospital for treatment. Examination on April 27, showed the patient to be a medium-sized, well-developed young man with good musculature, but emaciated. The skin of the chest and abdomen was pigmented (from Roentgen ray treatment). The patient had a temperature of 39° C.; pulse, 96; regular. The sternum, ribs and tibias were somewhat sensitive to pressure. The pupils reacted normally. Behind the left sternocleidomastoid were large packets of hard lymph glands that could be felt as separate nodes. In the right supraclavicular space was a walnut-sized mass. The left axillary glands were also enlarged. The chest showed increased dullness over the sternum, especially to the right. The area of relative heart dullness was normal. There was pain along the right sciatic nerve and the inguinal glands were enlarged on both sides. The knee jerk is increased, the Babinski sign negative. From April 30 to May 5, the patient received Roentgen ray treatment. On April 30, a blood examination showed: Red blood cells, 4,630,000; leukocytes, 18,000; neutro-

philes, 85 per cent; lymphocytes, 4 per cent; monocytes, 9 per cent; eosinophiles, 2 per cent. On June 19, the patient had a herpes zoster in the seventh right intercostal space. On June 23, the temperature rose to 40.5° C., with severe pain in the chest and a sense of pressure in the chest. After another series of Roentgen ray treatments the patient left the hospital on July 26, 1920. On November 20, 1920, he returned to the hospital with pains in the joints, attacks of renal colic, retention of urine and high fever. He was very pale and emaciated. On November 23, Roentgen ray treatment was begun. The fluoroscopic examination showed marked enlargement of the mediastinal masses. The patient left the hospital on December 1, and died two weeks later.

Summary of Case II. P. S. was found to have mediastinal and generalized lymphogranuloma at the age of twenty years, following repeated attacks of tonsillitis and a severe illness with scarlet fever. He became ill in August, 1917, and with Roentgen ray therapy lived until December, 1920, about three and a half years.

CASE III.—Mr. O. S., the son of Case I, is an engineering student, now twenty-seven years of age. He was born in Vienna where he lived for seven years; from the age of seven to twenty-one years, he resided in Teschen, Schlesien. He was in the military service from 1915 to 1918, in southern Hungary and Italy. For the past five years he has been studying in Vienna.

Past Illnesses. He had measles at six years of age. Has had frequent attacks of tonsillitis from childhood until about three years ago. These attacks occurred about every year, lasting two weeks or more. He had diphtheria twice, at eight and at fifteen years of age. He sustained a shrapnel injury of the right eye during the war, with a resulting corneal scar and loss of vision in this eye.

Present Illness. The present illness began in 1922, with coughing and pain in the chest for about three months. In March, 1923, a diagnosis of "apicitis" was made by a physician. He had at that time fever, sweats mostly at night, a tired feeling and cough. He went to the country for a three week's rest and returned somewhat improved. In April, 1923, he "caught a cold;" again he had a cough and fever. He remained in bed a few days. He then consulted a physician, who suspected the presence of a mediastinal tumor.

On July 2, 1923, the patient came to the Wenckebach Clinic for examination. The patient complained of a tired feeling and a sense of pressure in the chest. He was a medium-sized, well-developed young man, pale, with little subcutaneous fat. On the face and trunk were a number of vaguely outlined small brownish pigmented areas. The skull was normal. There was a corneal scar in the right eye. The left pupil reacted normally. In the left supraclavicular fossa was a chain of enlarged lymph nodes. There

were some enlarged deep cervical glands along the left sternocleidomastoid muscle, but none were palpable on the right side. The axillary and inguinal glands were not enlarged. The patient had a chronic pharyngitis with greatly enlarged tonsils. The ears were normal. There was no evidence of accessory sinus disease (Report of the Neumann Ear Clinic). The thyroid was somewhat enlarged, symmetrical.

On percussion of the thorax one found a broad area of dullness in the mediastinum which extends about 5 cm. to the right of the sternum, to a less extent to the left of the heart dullness in the region of the great vessels. The dullness could also be demonstrated on the posterior wall of the chest, to the right of the spinal column. There was dullness of the left apex. Tactile fremitus was somewhat reduced over the left upper lobe area, with bronchial breathing, and a few crepitant râles over the left apex. The movements of the diaphragm were normal. The heart was free from murmurs, its size difficult to determine because of the areas of dullness already mentioned. The radial pulses were equal, 80, regular. In the abdomen there were no palpable tumor masses, but the spleen was palpable.

A blood examination on July 3, 1923, showed: Red blood cells, 4,500,000; hemoglobin, 85 per cent; leukocytes, 12,700; neutrophiles, 75 per cent; lymphocytes, 8 per cent; monocytes, 12 per cent; eosinophiles, 4 per cent; myelocytes, 1 per cent. Fluoroscopic examination of the chest revealed a large mediastinal tumor extending to the right and to the left of the heart shadow. Its outline was sharp, and it had a lobulated appearance. It was especially marked about the right hilus and to the left of the great vessels. The left apex and the upper part of the left lung were darker than the right. The movements of the diaphragm were normal. There was no evidence of pleuritis (see Roentgen ray photograph of Case III). The patient received six Roentgen ray treatments and left the city for the summer.

On September 26, 1923, he returned and a Roentgen ray picture of the chest showed the mediastinal growth greatly reduced in size. The left upper part of the lung had cleared up. A large gland in the left axilla was still palpable. A blood examination showed: Leukocytes, 11,000; neutrophiles, 76 per cent; lymphocytes, 10 per cent; monocytes, 9 per cent; eosinophiles, 5 per cent.

Since September, 1923, the patient has received Roentgen ray treatment every four months (neck, front and back of chest) and has felt quite well, being able to continue his work. During the treatment his temperature rose to 39 in the evening, afterward his temperature was usually normal. In July, 1925, the patient noticed that the glands in the left supraclavicular space increased considerably in size, and he developed radiating pains in the left arm. In October severe pain in the back and right arm set in so that the

patient could not sleep at times. He also has pain in the left chest. The temperature rises evenings to 38° or a little above. The appetite is poor. On October 26, 1925, the patient completed a series of Roentgen ray treatments and the glands have become much smaller, the pains have disappeared, except for a dull pain in the cardiac region especially on the left side. The Roentgen ray examination shows the heart to be considerably enlarged, especially to the left. There is a slight pleural effusion on the left side. The mediastinal masses are visible but considerably smaller. Examination of the urine is negative; the blood pressure is 120 systolic. The liver and spleen are enlarged. Blood examination on October 26, showed: Red blood cells, 3,800,000; leukocytes, 6100.

Summary of Case III. This patient, twenty-seven years of age, developed mediastinal lymphogranuloma three years ago. He had suffered frequently from throat trouble and attacks of tonsillitis. The present illness began with cough and pain in the chest, fever, sweats, pigmentation and loss of strength. On examination a large mediastinal tumor was found accompanied by enlargement of the cervical and axillary glands. Roentgen ray treatments caused the mediastinal masses to disappear almost entirely, and the glands to reduce in size. Since December, 1925, the patient's condition has become worse, he has lost considerable in weight and strength, has developed an enlargement of the heart, a pleuritis, and pains in the back and upper extremities.

The patient returned to the clinic on December 14, 1925, with marked dyspnea, pain in the chest, and edema of the legs. Examination reveals a pleural effusion on both sides of the chest. The heart dullness is greatly enlarged to the right as well as to the left, and suggests a pericarditis with effusion. The Roentgen ray examination (Fig. 4, Case III) shows a bilateral pleural effusion with a very large heart shadow. Knowing the patient for some time, and failing to find any evidence of valvular disease I made the diagnosis of extension of the lymphogranuloma to the pleura and pericardium, with possible involvement of the myocardium. The patient died on December 22, 1925, and the autopsy confirmed the diagnosis.

The autopsy, performed by Dr. Matras of the Pathological Institute, University of Vienna, Prof. R. Maresch, showed the following: There is a hemorrhagic effusion in both pleural spaces. The lungs are heavy and dark red. The left apex contains an anthracotic indurated scar of healed tuberculosis. There is marked passive congestion of the lungs with embolic hemorrhagic infarcts, chiefly in the right lower lobe. The anterior mediastinum is occupied by a very dense nodular grayish-white tissue mass in the thymus region. The mass covers the enlarged pericardium and fuses with the mediastinal pleura of the left lung, extending over the latter. The mass reaches a considerable thickness on the diaphrag-

matic surface of the pericardium. The hilus region of both lungs is also infiltrated. The white firm scar-like tissue extends along the main bronchi into the lung tissue, especially on the left side. From the left hilus a thick band extends into the posterior mediastinum to the diaphragm. On the right side the diaphragmatic pleura is extensively infiltrated and the surface nodular. There are hard infiltrated glands along the trachea and esophagus.

The pericardium contains about 700 cc. of a clear yellowish fluid. Both ventricles are enlarged. Both auricles appear small on account of compression by a number of hard nodules up to the size of a walnut, originating from the inner surface of the pericardium and protruding into the sac. The left auricle is compressed from behind and in front, the right chiefly at the entrance of the vena cavas. The walls of both auricles are infiltrated especially the right. There are small nodules along the superior vena cava. The lumen of the superior vena cava is greatly reduced, that of the inferior less so. Along the sinus transversus pericardii is a band of infiltration uniting the nodules in the two auricles. There are also nodules in the adventitia of the pulmonary artery. The infiltration also extends into the subepicardial fat of the ventricle.

There is fatty infiltration of the liver. There are isolated small whitish infiltrations in the kidneys.

The spleen contains numerous small nodules. There is a fresh thrombosis of the veins of the left leg extending to the inferior vena cava. There is hyperplasia of the lymph follicles of the spleen and intestines. The urogenital tract is normal as also the pancreas, adrenals, and brain. The axillary, inguinal, mesenteric, and retroperitoneal glands appear unchanged.

Histologically the tumor is a lymphogranuloma rich in connective tissue. The character of the specific granulation tissue is altered through a great increase in connective tissue and reduction in the number of Sternberg giant cells, most likely due to the repeated Roentgen ray treatments.

Anatomical Diagnosis. Lymphogranuloma of the anterior mediastinum in the thymus region with extension into the posterior mediastinum, peritracheal and peribronchial connective tissue, pericardium and myocardium. Compression of both auricles, superior and inferior vena cava. Lymphogranuloma of the pleura, epicardium, tracheobronchial paratracheal and esophageal glands, spleen and kidneys. Marked passive hyperemia of the lungs, liver, kidneys and spleen. Thrombosis of the left crural, femoral and iliac veins. Multiple hemorrhagic infarcts of the lungs. Bilateral hydrothorax, hydropericardium and slight ascites. Healed tuberculosis of the left apex.

Summary and Conclusions. Two cases are reported of mediastinal lymphogranuloma, and one of "mediastinal tumor" probably also a lymphogranuloma, in one family, all three men. The first patient

died of mediastinal tumor in 1899 at the age of thirty-four years. His nephew (brother's son) died in 1920, twenty-one years later, of mediastinal lymphogranuloma at the age of twenty-three years. The son, now twenty-seven years of age, has been suffering since 1922 of a mediastinal lymphogranuloma. It developed twenty-three years after the death of the father. It is difficult to explain these 3 cases as being due to infection from a common source because of the long interval between the death of the first patient and the development of the disease in the two younger persons. The two latter have developed the disease at about the same age, one at twenty-two and the other at twenty-four years. Furthermore, the son and nephew never lived together. At the time of the father's death his son was only one and a half years of age, and the nephew only two years of age. We may assume a familial predisposition to mediastinal Hodgkin's disease in these cases, possessed by the three male members of the family.

Can the virus of Hodgkin's disease enter the body and remain dormant for years before causing symptoms of the disease? This question we are at present unable to answer as we do not yet know the cause of the disease.

We have evidence that individuals with status lymphaticus are more susceptible to certain infectious diseases, and it is possible that such persons are also more susceptible to lymphogranuloma. Furthermore, the fact that mediastinal lymphogranuloma often arises in the thymic tissue suggests the possibility that a condition of status thymicus or a persistent thymus predisposes to infection. Perhaps we can explain the occurrence of 3 cases of mediastinal lymphogranuloma in males of the same family, by assuming that all 3 possessed a persistent thymus, which condition, hereditarily transmitted, predisposed them at the ages of thirty-four, twenty-two, and twenty-four years, to infection with Hodgkin's disease.

Two of the patients suffered with repeated attacks of tonsillitis and had greatly enlarged tonsils. I have observed in a high percentage of cases of lymphogranuloma tonsillar enlargement, and it would seem that such chronic inflammations of the lymphatic apparatus either predisposed the individual to the disease, or mark the onset of the infection with the unknown virus of the disease.

I have discussed the predisposing causes of Hodgkin's disease and called attention to the greater prevalence of the disease in males than in females. I have found no relation to occupation. The disease is most common from the twentieth to the fortieth year.

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THE PATHOGENESIS OF DEATH FROM BURNS.

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We observed 2 fatal cases of first degree burns in children, with striking changes in the blood-sugar content.

Case Reports. CASE I.—L. R., aged two years, was admitted to the United Israel Zion Hospital of Brooklyn on January 16, 1925, with a first degree burn contracted by playing with matches and involving the right buttock and the upper part of the right thigh. The burn was of twenty-four hours' duration and the child received no treatment until his admission to the hospital. Examination of the child on admission at 9 A.M. revealed the following: The pupils were dilated and reacted sluggishly to light; the abdomen was very much distended; the child appeared toxic, and the skin was of a grayish color. He presented a superficial burn with vesicle formation of the right buttock and upper one-third of the thigh. On the evening of the same day the child became semicomatose and developed clonic seizures. On the following day, January 17, at 10 A.M., examination revealed the following: The child appeared very toxic; the heart beat was very rapid and the sounds were of poor quality, the first sound being barely audible; the respirations were very rapid and superficial; there was a distinct odor of acetone to the breath. A 10 per cent solution of glucose was given intravenously, and 8 minims of a 1 to 1000 solution of adrenalin chloride were injected subcutaneously every two hours. The child grew progressively worse and died at 3 P.M. on the same day. The temperature, which was 102° F. on admission, rose to 103° F. in the evening of the same day and showed a very marked rise to 106° F. immediately before death. Examination of the urine showed acetone and diacetic acid, but was otherwise negative. Microscopic examination of blood revealed a total red blood count of 4,000,000, and a hemoglobin content of 80 per cent. The total white blood count was 17,000, of which 75 per cent were polymorphonuclear leukocytes. Chemical examination of the blood, made on January 16, showed an entire absence of sugar.

CASE II.—J. S., aged three years, was admitted to the hospital on February 7, 1925, with the following history. On February 2 he fell into a bath tub containing hot water and received an extensive superficial burn, involving the left side of the chest, the left leg and the inner surface of the right thigh. The child was treated at home for five days, during which time the temperature ranged from 100° F. in the morning to 103° F. in the afternoon. In addition to local treatment the patient was given glucose *per os* and *per rectum*. On the morning of February 7 he manifested a fine tremor and muscle twitchings, and the family physician advised hospitalization. Examination of the patient on February 7 at 8.30 A.M. revealed the following: A superficial burn involving the left side of the chest, the left leg and the inner surface of the right thigh; the abdomen was distended and tympanitic on percussion; the skin was of a bluish-gray tint; respirations were of Kussmaul type, and there was a distinct odor of acetone to the breath; the pulse was very rapid, 168 beats to the minute, and of poor quality; the child had

clonic twitchings involving the upper extremities, and the sensorium was clouded. Two hundred cubic centimeters of a 10 per cent solution of glucose were given intravenously. At 4 P.M. of the same day the temperature rose to 104° F., and all the foregoing symptoms became aggravated. Exsanguination and transfusion, as advocated by Robertson and Boyd,[1] were attempted, but it was not possible to remove more than 50 cc. of blood. This was due probably to the lowered blood-pressure and the increased concentration of the blood. One hundred cubic centimeters of blood from a donor were given. During the transfusion the patient became cyanotic and had a severe chill; following the chill the child became comatose. At 8 P.M. the temperature rose to 108° F., and the child died at 9.50 P.M. Examination of the fluid obtained by spinal puncture immediately before death revealed no trace of sugar. Examination of blood removed from the heart immediately after death showed a blood-sugar content of less than 30 mg. per 100 cc. of blood.

A necropsy was not obtained in either case.

Although adrenalin in fairly large doses was administered hypodermically to both patients, and glucose was given intravenously and through other channels, chemical examination of the blood revealed an entire absence of sugar in the first case and a very low sugar content in the other. This was a rather striking finding in view of the fact that Underhill[2] found an increased concentration of the blood in a series of burn cases. One would expect a rise in the blood-sugar content in proportion to the concentration of the blood. As a matter of fact Underhill found blood-sugar values in his patients, ranging from 98 mg. to 216 mg. per 100 cc. of blood.

Our findings lead us to believe, however, that in addition to the disturbance in the water metabolism which occurs, as shown by Underhill, a definite disturbance also takes place in those organs which are concerned with the regulation of the blood-sugar content. In order to study the blood-sugar levels in burns and the effects of the burns on the organs most concerned in the regulation of the blood-sugar levels, namely, the suprarenals, the liver and the pancreas, we produced burns in rabbits. We chose the rabbit because we considered this animal most suited for this type of work. The burns were produced while the animals were etherized, and all precautions against unnecessary suffering were taken. The animals were subsequently carefully observed and were apparently free from pain.

The blood-sugar content was determined by the method of Folin and Wu[3] in each animal immediately before the burn, one-half hour after, one and a half hours after, four hours later, twelve hours later and then every twelve hours thereafter. The blood, withdrawn with a sterile needle from the heart, was examined immediately. The

animals lived for from four hours to several days, depending upon the degree and severity of the burns produced. Immediately after death the liver, suprarenals, pancreas and some muscle tissue were removed. The liver, pancreas and suprarenals were examined histologically; the glycogen content of the liver and muscle tissue was determined chemically, using the liver of a normal rabbit as a control.

The following method for the glycogen determinations, as first described by Pflüger,[4] was employed. The liver was removed *in toto* and weighed. One hundred grams of finely divided liver or muscle tissue, removed immediately after death to obviate postmortem conversion of the glycogen content, were boiled in 100 cc. of a 60 per cent solution of potassium hydroxid for two hours. The solution was made up with water to 400 cc., allowed to sediment at room temperature and then filtered through glass wool until clear or weakly opalescent. One hundred cubic centimeters of the filtrate were mixed with an equal volume of 96 per cent alcohol to throw down the glycogen. After complete precipitation of the glycogen it was allowed to stand overnight. The mixture was filtered through a Swedish filter. The retained glycogen was washed repeatedly with a mixture containing 1 volume of a 15 per cent solution of potassium hydroxid and 2 volumes of 96 per cent alcohol; it was finally washed with 96 per cent alcohol. The funnel was then filled with sterile cold water and allowed to stand. The glycogen, being soluble in water, was entirely forced through by repeated washings. The solution was neutralized with 25 cc. of hydrochloric acid, having a specific gravity of 1.19, and made up to 500 cc. with water. The flask was then heated in a boiling water bath for three hours, thus converting the glycogen to glucose. The amount of glucose was then determined by the method of Folin and Wu.

The following table describes the blood-sugar determinations made in 7 of the rabbits employed in the experiments, and gives also a brief description of the degree and extent of the burns produced (Table I). The blood-sugar content of rabbits Nos. 1 and 2, although determined, are not included because the results are questionable, due to the fact that after the determinations were made we found an inaccuracy in the colorimeter.

Glancing over the curves, it is at once evident that a marked rise occurred uniformly in all rabbits shortly after the burns. The blood-sugar content begins to rise one-half hour after the burn and reaches the peak, as a rule, one and a half hours later, the highest level being 500 mg. per 100 cc. of blood and occurring in rabbit No. 7 (Chart IV). The increase in blood sugar ranges from 130 mg. to 380 mg., with an average increase of 170 mg. per 100 cc. of blood. The greatest rise occurred in the rabbits that were most severely burned and that presented the greatest manifestations of

shock. When the blood-sugar content was high and the rise occurred very suddenly, death, as a rule, followed. Rabbits Nos. 4 and 5 died in from two to four hours (Table I). When the rise was not so marked the animal usually withstood the shock and lived for a longer period of time, finally succumbing to the later effects of the burns (Table I).

TABLE I.—BLOOD-SUGAR CONTENT OF RABBITS PER 100 CC. BLOOD (IN MILLIGRAMS).

Time after burn, hours.	No. 4.	No. 5.	No. 6.	No. 7.	No. 8.	No. 9.	No. 10.
Before	80	66	90	118	111	105	153
½ hour	77	100	142	220	153	180	240
1½ hours	333	400	222	500	200	222	240
4 "	...	333	200	80	250	222	333
6 "	...	...	190	...	...	200	
9 "	...	...	133				
24 "	...	...	133	285	100	190	222
36 "	...	...	60	...	153	200	250
48 "	...	...	110	...	181	222	222
72 "	...	...	133	...	...	...	222
Death occurred in	3½ hrs.	4 hrs.	75 hrs.	26 hrs.	52 hrs.	53 hrs.	72 hrs.

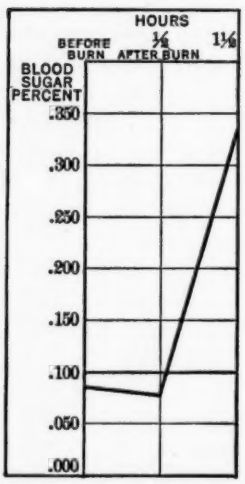

CHART I.—Sugar before and after burn in Rabbit No. 4.

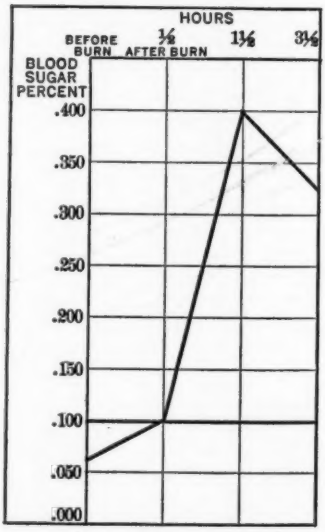

CHART II.—Rabbit No. 5.

In rabbit No. 6 (Chart III) there was a gradual decline of blood-sugar content after the initial rise, the lowest point of 60 mg. being reached thirty-six hours after the burn. Death did not occur until two days later. A blood-sugar determination three hours before death showed a content of 133 mg.

In rabbit No. 7 (Chart IV) the blood-sugar content reached the highest point of 500 mg. one and a half hours after the burn, and showed a marked drop to 80 mg. twenty-four hours later. The rabbit died forty-eight hours after the burn. Two hours before death the blood-sugar content again rose to 285 mg.

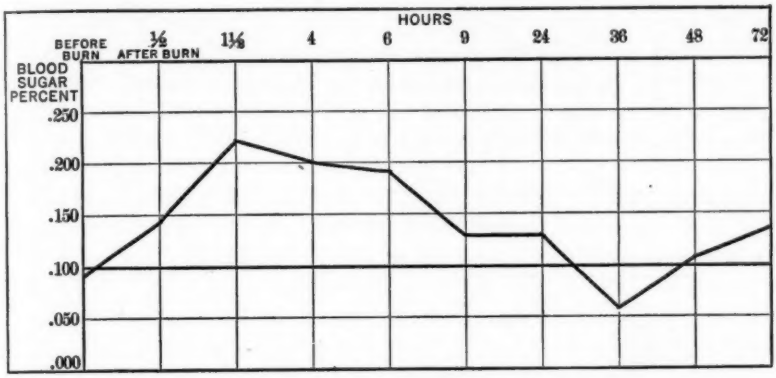

CHART III.—Rabbit No. 6.

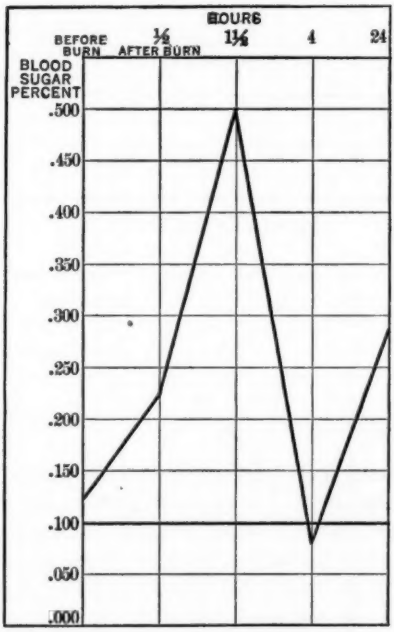

CHART IV.—Rabbit No. 7.

In rabbit No. 8 (Chart V) the blood-sugar content reached its peak of 250 mg. four hours after the burn, but declined rapidly to 100 mg. after twenty-four hours. The animal died twenty-four

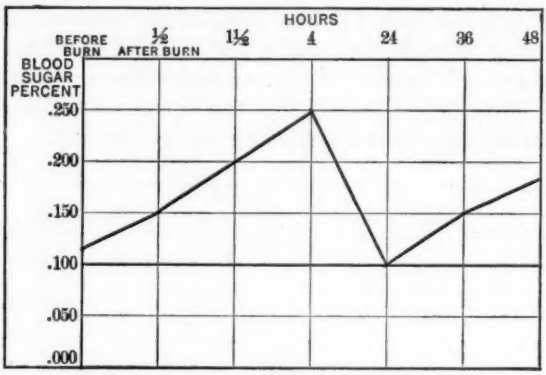

CHART V.—Rabbit No. 8.

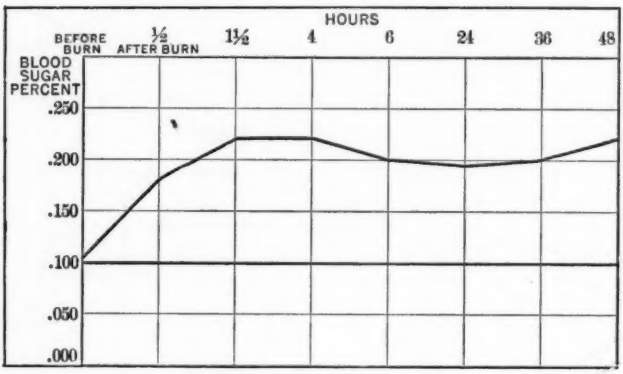

CHART VI.—Rabbit No. 9.

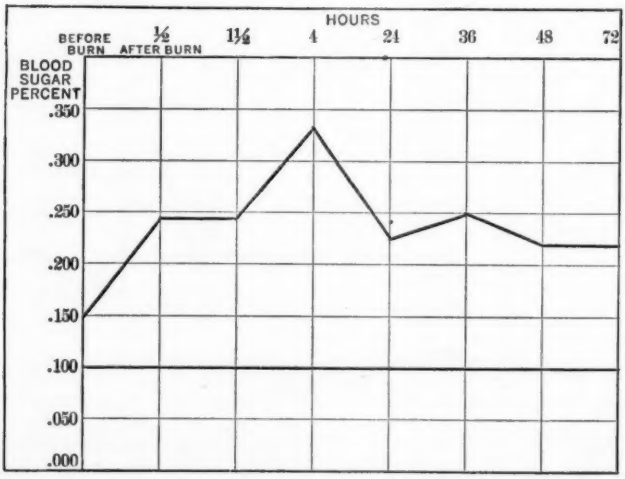

CHART VII.—Rabbit No. 10.

hours after the decline. The blood-sugar content four hours before death was 181 mg.

In rabbit No. 9 (Chart VI) the blood-sugar content reached the peak of 222 mg. one and a half hours after the burn. No noteworthy drop in blood-sugar content occurred in this rabbit.

In rabbit No. 10 (Chart VII) the blood-sugar content reached the peak of 330 mg. four hours after the burn, but a rise of 240 mg. had already occurred one and a half hours after the burn. Here a more gradual rise occurred and also a gradual decline from 330 mg. to 222 mg. within the next twenty-four hours. This animal died not from the results of the burn but from a subpericardial hemorrhage, due to heart puncture.

It can be seen that a marked drop from the initial rise occurred in 3 rabbits, with a secondary rise immediately before death (Charts III, IV, V). In 2 of the rabbits the drop was more gradual and no secondary rise occurred (Charts VI and VII). We wish to emphasize the fact that no animal died in a state of hypoglycemia, but, on the contrary, all the animals died in a state of hyperglycemia.

The glycogen determinations follow (Table II): The liver of the control animal, figuring on a basis of 100 gm. of liver tissue,

TABLE II.—GLYCOGEN CONTENT IN GRAMS PER 100 GRAMS OF SUBSTANCE.

Rabbit No.	Liver, gm.	Muscle, gm.
1	1.49	3.16
2[1]	0.63	1.97
3[2]	0.98	2.20
4	0.53	0.44
5	1.10	0.60
6[3]	0.35	0.27
7	0.50	2.00
8	1.10	0.33
9	1.60	1.30
10[4]	1.30	0.30

[1] Terminal convulsions.
[2] Slight convulsions.
[3] Autolysis.
[4] Terminal convulsions.

contained 0.98 gm. of glycogen. One hundred grams of muscle tissue of the control animal contained 2.2 gm. of glycogen.

Rabbits Nos. 4 and 5 (Charts I and II), which died in the period of high blood-sugar level, 333 mg., showed a decrease in the liver glycogen and an even more marked decrease in the muscle glycogen, so that it can be asserted that the decrease in the muscle glycogen is probably not due to a retention of glycogen in the liver. Rabbits Nos. 8 and 9 showed figures which are parallel to those of rabbit No. 5 in this respect, that the liver glycogen is fairly normal, but a marked decrease in muscle glycogen is seen. These animals also died in a state of hyperglycemia (Charts V and VI).

Histologic Examinations. (By Dr. Max Goldzieher, pathologist of this hospital.) The method employed in the histologic glycogen determinations was as follows: The liver was hardened in 95 per cent alcohol, and was stained with Delafield's hematoxylin stain and decolorized with acid alcohol; the slides were then stained with Best's carmine solution. It was found that this method was unsuitable for determining glycogen in the liver quantitatively, as there was no parallel between the quantities determined chemically and the amount of glycogen seen histologically. The liver presented a fairly normal appearance, except in rabbits Nos. 4, 7 and 8. In rabbit No. 10 the liver cells showed marked cloudy swelling, and, as a result, the intratrabecular capillaries were in great part narrowed or entirely occluded. Rabbits Nos. 7 and 8 showed narrowed, atrophic trabeculæ. In rabbit No. 4, which died two hours after the burn and showed a blood-sugar content of 333 mg. immediately before death (Chart I), the liver glycogen, determined chemically, was very low, 0.53 gm. per 100 gm. of liver substance. On the whole, however, it may be said that no conclusions can be drawn from the changes found in the liver microscopically in relation to the changes in the blood-sugar content.

All pancreases examined microscopically showed normal glandular structure. The islands of Langerhans were present in normal numbers and without changes, except in rabbits Nos. 9 and 10, where they were found to be quite large, although normal in number.

For the examination of the suprarenals, the following staining method was employed: The suprarenals were removed immediately after death and placed in a 5 per cent solution of potassium chromate for several days; they were then kept under running water for twenty-four hours and embedded in paraffin in the usual manner; they were stained with hematoxylin, decolorized with acid alcohol and finally faintly stained with eosin.

Rabbit No. 1. The medullary substance showed abundant deposition of chromium, and the cells stained with the brown stain were but slightly granular and rather homogeneous in character; under high power numerous drops of secretion stained yellowish-brown were seen; the bloodvessels of the medulla were dilated; the nuclei of the cells of the medullary substance took on the stain sufficiently well, but the borders of the cells themselves were somewhat indistinct; the cortex showed no definite changes, except that the middle zone showed a slight web-like structure. Microscopic diagnosis: Definite hyperactivity.

Rabbit No. 2. The bloodvessels of the medullary substance were markedly dilated and were filled with coagulated masses, which were not thrombi; the medullary cells showed a good deposition of chromium and contained numerous orange-colored drops of secretion or vacuoles, corresponding in size and shape to the drops seen; the cortex showed no extraordinary changes; increased lipoid con-

tent was seen only in the zona fasciculata. Microscopic diagnosis: Extreme hyperactivity.

Rabbit No. 4. The medullary substance was very well developed; the bloodvessels were dilated, and the ability of the cells to retain their chromium was distinctly maintained; it was noted that occasional cells contained very large drops of secretion, which took on an orange color when stained with a chromeosin stain, in marked contrast to the dark-brown granular cytoplasm; other cells showed marked vacuolation, the vacuoles corresponding in form and size to the above-mentioned drops of secretion; the cortex showed distinct formation of the strata; the zona fasciculata and zona reticularis consisted of strikingly large cells, which were markedly vacuoled and therefore took on a pale stain; the capillaries of the cortex were not distended. Microscopic diagnosis: Hyperfunction.

Rabbit No. 5. The capillaries of the medullary substance were markedly dilated; the medullary substance itself gave evidence of a marked diffuse chromium reaction; drops of secretion were seen only occasionally; the medullary cells were rather small; the nuclear stains were irregular and in some places quite pale; the cortex showed the usual structures; the cells of the zona fasciculata stained quite pale, whereas in the zona reticularis the protoplasm of the cells was intensively stained. Microscopic diagnosis: Incipient exhaustion.

Rabbit No. 6. Microscopic examinations of the liver, pancreas and suprarenals of this animal were not made because of autolysis.

Rabbit No. 7. There was a striking disassociation of the structure of the medullary substance, caused by edematous stroma; the deposition of chromium was irregular and good only in patches; drops of secretion were abundant and were equal to or exceeded in size the nuclei of the cells; they took on a deeper brown stain than the granules containing chromium; the periphery of the cortex showed only in patches the structure of the zona glomerulosa; the nuclei of the cells were absent in a wide strip, corresponding to the border of the zona fasciculata, and in this area the borders of the cells were obliterated; many bacterial emboli, consisting of staphylococci, were found in this necrotic area; otherwise there were no noteworthy changes in the zona fasciculata and zona reticularis. Microscopic diagnosis: Transitional medullary injury, with evidences of regeneration of function.

Rabbit No. 8. The medullary substance showed markedly dilated capillaries and distinct edema; the deposition of chromium could be seen only in occasional cells and drops of secretion were seen only occasionally; the borders of the cells were obliterated; the cortex showed a normal structure of the strata, although in wide areas the structure was completely destroyed and the nuclei were unstained; there were many bacterial emboli in the necrotic areas. Microscopic diagnosis: Severe medullary injury; secretory function partially retained.

Rabbit No. 9. The medullary substance showed only slight deposition of chromium, most cells remaining unaffected; there was a perinuclear, diffuse yellow stain without distinct granules only in patches; drops of secretion were rare; otherwise the structure of the medullary cells was well retained; there were everywhere nuclei that were sufficiently stained, although the nuclei in wide areas of the cortex, particularly in the zona fasciculata, were only very weakly stained; the cells in the zona glomerulosa were well stained; the borders of the cells of the cortex were retained even in those areas where the cells did not take the stain; the cells showed a web-like structure due to a marked degree of vacuolation. Microscopic diagnosis: Retention of lipoids in the cortex with mild exhaustion.

Rabbit No. 10. The examination of the medullary substance showed a diffuse chromaffin reaction without evidences of granule formation; drops of secretion were very scant, although there were many vacuoles; the outline of the cells was very indistinct and the nuclear stain was in part indistinct; the differentiation of the three layers of the cortex was barely discernible; the vacuolation of the cells of the cortex was quite marked and evenly distributed; the cells were large and pale; in the zona reticularis there were areas of small cells that showed no vacuolation, and therefore took a deeper stain. Microscopic diagnosis: Beginning slight exhaustion of secretory function of the suprarenals.

Conclusions as to the Microscopic Findings of the Suprarenals in Relation to the Blood-sugar Content. *Rabbit No.* 1. The histologic examination of the suprarenals showed that this rabbit was killed while the glands were in a state of hyperactivity. This animal was the only one in the series that was killed, except the control rabbit.

Rabbit No. 2. Histologically the suprarenals were in a state of very marked hyperfunction when death occurred; this agreed with the clinical course of the animal, which died in shock three and a half hours after the burn was produced; the blood-sugar determinations showed a marked rise.

Rabbit No. 4 (Chart I). The suprarenals of this animal, which died in a state of hyperglycemia with a blood-sugar content of 333 mg., showed evidences of very marked hyperfunction. This points to the fact that shortly after the burn occurred a severe strain was placed upon the suprarenals with an outpouring of adrenalin into the blood. Hyperadrenalinemia was evidenced by the high blood-sugar content and the low-glycogen content of the liver (0.53 gm.).

Rabbit No. 5. The suprarenals of this animal showed evidences of beginning exhaustion, agreeing with the blood-sugar finding of 233 mg., determined one-half hour before death, in contrast to the blood-sugar finding of 400 mg. determined one and a half hours after the burn. It is quite probable that the suprarenals were in

the same state of hypersecretion as in rabbit No. 4, but, owing to the fact that this rabbit lived longer, destructive changes took place in the suprarenals, as evidenced by the drop in the blood-sugar content. The glycogen content of the liver, 1.1 gm., also bears out this conclusion.

Rabbit No. 7. Histologically there was transitional injury of the medullary substance with evidence of regeneration of the secretory function. The blood-sugar content, determined one and a half hours after the burn, was 500 mg. (Chart IV). Apparently a great strain was placed upon the suprarenals as a result of the shock and destructive changes probably occurred shortly after in the medullary substance. This was also substantiated by the blood-sugar finding of 80 mg., determined four hours after the burn (Chart IV). Apparently regeneration began to take place, for twenty hours after the last blood-sugar determination a final determination showed a content of 285 mg. This was also borne out by the low-glycogen content of the liver, 0.5 gm., and also by the microscopic finding in the suprarenals.

Rabbit No. 8. Severe injury to the medullary substance with a partial regeneration of secretory function was substantiated by the blood-sugar finding of 250 mg. four hours after the burn (Chart V). Here too an outpouring of adrenalin into the blood probably occurred. The subsequent rapid decline to 100 mg. was due probably to the marked degenerative changes present in the medullary substance and the impaired secretory function. With the regeneration of the secretory function the blood-sugar content rose, but more gradually and not to a level high enough to change materially the glycogen content of the liver.

Rabbit No. 9. This rabbit died while the glands were in a state of mild exhaustion; blood-sugar content showed no decline below the normal at any time, nor was there a premortal rise above that which occurred four hours after the burn.

Rabbit No. 10. Mild exhaustion of the secretory function was accompanied here by a rise in the blood-sugar content, although this animal normally had a somewhat higher count than the other rabbits. The decline was also gradual. These blood-sugar findings lead us to believe that death occurred while the suprarenals were still in an incipient state of hypersecretion, and that although the suprarenals showed beginning exhaustion, as evidenced by the weakly stained nuclei, death occurred very suddenly after puncture of the heart and was actually due to hemorrhage.

Comment. The causation of death in burns has been a mooted question; it is generally accepted, however, that it is caused by the absorption of toxins from the burned area. These toxins are supposed to be primary and secondary proteoses, absorbed into the blood stream.

Robertson and Boyd[5] found parenchymatous degeneration of the

abdominal organs and believed that these changes were produced by an absorption of toxins from the burnt areas.

Weisskotten[6] reported necropsy findings in a series of 10 burn cases, 5 occurring in children and 5 in adults. He found that the most marked pathologic changes occurred in the suprarenals, with but slight changes in the liver and practically no changes in the pancreas. He found almost uniformly that hemorrhages and necrosis occurred in the suprarenals in those cases that died of the primary shock in from four to five hours after the burn, and found practically the same changes in those cases that survived the initial shock and died in from two to six days after the burn. He reported also that the gland cells were pale staining and very much swollen. Many were apparently undergoing hydropic degeneration. Necrotic cells, being invaded by polymorphonuclear and endothelial cells, were not infrequent. The whole process was quite diffuse.

Olbrycht[7] stated that in his experiments in burns on rabbits and dogs he found pathologic changes occurring only in the suprarenals. These changes were hyperemia and ecchymosis and reduction or total loss of the chromaffin substance and lipoids. He ascribed the changes to a toxic action from decomposition of the protein in the burnt tissues, and his conclusions were that devitalized protein in the burnt area had to be cleared out and that the suprarenal function had to be stimulated or substituted by epinephrin.

Since we were interested only in those organs concerned with sugar metabolism, we gave our attention solely to the suprarenals, pancreas and liver. As before mentioned, no marked deviations from the normal were found in the liver or pancreas. The most definite changes occurred in the suprarenals. In none of our cases was hemorrhage of the suprarenals with marked destructive changes in the tissues found. On the contrary, in those animals that died within three to four hours after the burn increased cellular activity was found. Only in those animals that survived the initial shock and lived for a period of from twenty-four to forty-eight hours after the burn were degenerative changes found, and then practically always with evidence of regeneration.

Bedford,[8] in a series of experiments on dogs and rabbits, found that shock increased the quantity of adrenalin which is normally thrown into the blood stream. This increased amount of adrenalin was accompanied by hyperactivity of the suprarenals, and was not simply the result of a release of epinephric material stored in the glands. This coincides with our findings in rabbits Nos. 2, 4 and 5, which died in two, three and a half and four hours, respectively, after the burns, and whose suprarenals showed evidences of marked hyperfunction histologically. The blood of these animals showed a sharp, marked rise in the sugar content, rabbit No. 2 showing the

most marked hyperglycemia, rabbits Nos. 4 and 5 not quite so marked, yet reaching a level of 400 mg. (Table I).

In view of the foregoing observations we think it logical to divide the causes of death from burns into two groups:

The first group comprises those cases in which death occurs shortly after the burn, before any considerable amount of toxin can be absorbed and can produce definite degenerative changes in the various organs of the body. These cases present a high blood-sugar content, death being preceded by a sudden, marked, sharp rise in the blood-sugar content, and being due most likely to changes in the sympathetic nervous system, because of shock produced by the burn. The effect of the shock of the burn on the sympathetic nervous system probably produces changes in the innervation of the suprarenals with a stimulation of the secretory functions of these glands, resulting in an outpouring of epinephrin into the circulation. As a matter of fact, the glycogen content of the livers in rabbits Nos. 2 and 4, both of which animals died in a state of shock, is very low. Although in rabbit No. 5 the glycogen content of the liver was not reduced, there was a marked decrease in the glycogen content of the muscle (0.6 gm.). These facts bear out the foregoing assumption.

The second group comprises those cases in which death does not occur until at least twenty-four hours or more after the burn has elapsed. In this group belong the cases which show a low blood-sugar level, some manifesting a temporary hypoglycemia. It is at this stage that the destructive changes manifest themselves in the suprarenals. It is quite probable that because of these changes a decreased amount of adrenalin is thrown into the blood stream, thus inhibiting the liver in its normal glycogenolytic function. This is also borne out by the fact that animals dying in this state show a higher liver glycogen content (Table II). It seems unlikely to us that death in this stage was due solely to the changes in the suprarenals with their altered functions. It is quite likely, indeed, that changes occur in other organs as well, but histologic examination of the liver and pancreas in our experiments fail to show any important changes from the normal.

A similar observation can be made in the case of burns in man. Death may occur in shock shortly after the burn or may follow after a longer period because of degenerative changes in the parenchymatous organs, particularly the suprarenals. If we can apply conclusions drawn from the experiments on the rabbit to similar cases in man, then we may say that during the stage of initial shock, where we found a hyperfunction of the suprarenals in the rabbits, adrenalin is contraindicated. Further experiments will have to be carried out to substantiate this theory.

In the second stage, however, where we find degenerative changes in the suprarenals which probably cause a diminution in the adrena-

lin secretion, adrenalin in fairly large and frequent doses is indicated. Glucose is to be given only in the second stage, and then in large doses with large amounts of fluid.

In the 2 clinical cases reported death occurred while the patients were in a state of hypoglycemia, whereas the rabbits died in a state of hyperglycemia. Although a drop in the blood-sugar content occurred within twenty-four hours after the burn in the rabbits, there was always an increase for several hours before death, all rabbits showing a definite hyperglycemia, some more marked than others. There exists a definite parallel between the functional state of the suprarenals, as determined by the histologic examinations, and the blood-sugar content. In every case where a diagnosis of marked hyperfunction of the suprarenals was made the blood-sugar content was extremely high.

Summary. 1. Two clinical cases of burns are reported with marked changes in blood-sugar content, that is, hypoglycemia.

2. Experiments on 10 rabbits were carried out to study the effects of superficial burns on the blood-sugar content of the organs concerned with carbohydrate metabolism.

3. In rabbits the cause of death may be divided into two stages: (*a*) Initial stage, due to shock, which is accompanied by a high blood-sugar content due to hyperactivity of the suprarenals; (*b*) secondary stage, due to degenerative changes, particularly in the suprarenals.

4. The administration of adrenalin is to be restricted only to the secondary stage of suprarenal exhaustion, and is contraindicated in the primary stage.

(We desire to express our thanks to Dr. Henry M. Feinblatt of this hospital, who first observed and called to our attention the marked hypoglycemia in the two patients described in the article.)

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STUDIES ON INTRA-ABDOMINAL PRESSURE.*

I. Negative Intra-abdominal Pressure as a Normal Condition.

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While working on the subject of paralytic and spastic ileus I found that several factors concerned with normal peristalsis in the small intestine were not adequately treated in the literature. Believing that the main problem could not be successfully approached until these factors were clearly understood, I have undertaken the following preliminary investigation.

It is the purpose of this paper to deal with one of these factors, intra-abdominal pressure. Measurements of the intra-abdominal pressure in living and dead animals and man, changes in intra-abdominal pressure induced by changes in the size of the abdominal cavity, and the reëstablishment of normal intra-abdominal pressure under certain conditions, are considered. The relation of intra-abdominal pressure to intra-thoracic pressure and the excursions of the diaphragm will be the subject of a second paper, while the relation of intra-abdominal pressure to normal and abnormal peristalsis of the small intestine will be treated in a third.

By intra-abdominal pressure is meant that pressure existing within what is anatomically termed the peritoneal cavity, including both the lesser and greater cavities. This cavity is generally described as a potential or capillary space existing between the visceral and parietal peritoneal surfaces; it is bounded above by the inferior surface of the diaphragm and below by the pelvic floor. There is reason to believe that an actual cavity or cavities of ever varying size, shape and position are present between the peritoneal surfaces.

The pressure within the abdominal or peritoneal cavity of a healthy animal breathing quietly is subatmospheric or negative. Concerning the existence, under ordinary conditions, of a negative intra-abdominal pressure little can be found in the English or French literature. The more recent German literature, however, contains several papers on the subject.

That intra-abdominal pressure is normally negative is satisfactorily demonstrated by clinical observations and laboratory experiments.

* Read before the Philadelphia Physiological Society, March 16, 1925.

Clinical Observations.—If a female patient be placed in the Trendelenburg position (pelvis elevated, thorax lowered) there will frequently be heard a rush of air into the unopened abdominal cavity; air is sucked into the abdomen through the vagina, uterus and patent Fallopian tubes. Likewise the observant surgeon has often noted a rush of air into the abdomen when, in a relaxed patient, the peritoneum is nicked. Noteworthy also is the operative procedure of distending the urinary bladder with air by inserting a stiff catheter and then lowering the patient's head and thorax.

Experimental Data. Measurements of intra-abdominal pressure are recorded in the literature. Luciani[18] (1878) and Rosenthal (1880) obtained measurements of what they considered intra-abdominal pressure by the use of rectal and esophageal sounds connected to a Marey tambour. Adamkiewiez and Jacobsen[1] and Rosenthal[25] determined the intra-abdominal pressure of the rabbit by means of the rectal sound, and found it to be −40 mm. of water in normal inspiration and −250 mm. of water in forced inspiration with the trachea closed. Numerous other investigators have employed the gastrointestinal sound or balloon in animals and man. The readings obtained have been taken to represent intra-abdominal pressure directly or to do so after being subjected to various hypothetical corrections. It is obvious that pressures existing within a living, contractile, hollow viscus do not represent the pressures exerted on the outside of that organ.

Several methods are available, for the direct measurement and demonstration of the negative pressure existing within the abdominal cavity.

I. An anesthetized dog was placed on his back, a midline abdominal incision was made down to, but not through, the peritoneum. The skin and muscles were reflected back on either side, creating a trough. This was filled with colored water; through the layer of water a pin-hole was made in the peritoneum. Gradually the solution was aspirated into the abdomen.

II. Anesthetized or unanesthetized dogs were placed on their backs. A hollow needle attached to a rubber tube, the free end of which dropped into an open-mouthed Erlenmeyer flask containing 150 cc. of colored water, was plunged through the anterior abdominal wall in the epigastrium. Care was taken to have both needle and tube filled with the colored water before insertion. Care was likewise taken to keep, at all times, the flask and water level well below the level of the inserted needle point, so as to eliminate any syphon action. In the five experiments made in this manner water in amounts varying from 50 to 120 cc. were aspirated into the abdomen within a five-minute period. At the end of this period the abdomen was opened and the fluid found in the dependent portions of the abdominal cavity. The presence of the fluid ruled out absorption as an activating force.

The amounts of fluid aspirated by the animals varied with the size of the animal and its type of breathing. The larger the animal the more fluid taken; the deeper and more rapid the breathing, the greater the amount of fluid aspirated. Lean animals took more fluid than did the obese.

III. If a hollow needle attached by rubber tubing to an open U-tube water manometer be thrust through the abdominal wall of man or animal, the degree of pressure present in the abdominal cavity can be read directly from the excursions of the water columns.

In the following experiments the same apparatus was used. It consisted of a hollow 16-gauge needle, thick-walled, rubber tubing of a 3-mm. bore and a U-tube water manometer constructed of 4-mm. glass tubing. The distance from the tip of the needle to the water surface was 30 cm. By using such a standard apparatus all pressure readings are comparable, excepting for the negligible variation of temperature.

It was found that the intra-abdominal pressure readings fluctuated with the phases of the respiratory cycle. Both the maximum and minimum pressures were noted and recorded. For simplicity and graphic representation these are written as a fraction. The minimum reading is written as the numerator and the maximum as the denominator of the fraction. If both readings are negative the fraction is preceded by a single minus sign. If one is positive and the other negative each factor is preceded by the corresponding sign. The values are recorded below.

IV. By substituting for the water manometer in the above experiment a Marey tambour with a writing point against which moves a smoked paper, a graphic record of all changes in pressure may be obtained. Calibration of the tambour at the end of the experiment makes possible measurement of the pressure changes recorded on the graph.

Water manometers equipped with a float and bearing a stylus were substituted in some experiments for the Marey tambour. They were found less satisfactory than the tambour.

All of the above experiments can be, and frequently were, performed upon unanesthetized animals. The thrusting of the needle through the abdominal wall is a simple procedure unaccompanied by pain. The difficulty of the method lies in the occasional occlusion of the distal end of the needle by the omentum. This can be overcome by gentle manipulation of the needle. The usual point of insertion of the needle was in the midline of the epigastrium. It was inserted, however, in many other locations. Records were made with the animals in various positions.

Readings in Living Animals. The following are average intra-abdominal pressure readings, made by Method III, upon various animals in the supine position.

1 small female monkey, $-\frac{2}{4}$* mm. water; quiet breathing; ether.
1 large male monkey, $-\frac{4}{6}$* mm. water; quiet breathing; ether.
6 rabbits, $-\frac{30}{5}$* mm. water; quiet breathing; no anesthesia.
6 cats, $-\frac{8}{14}$* mm. water; quiet breathing; no anesthesia.
100 dogs, $-\frac{20}{44}$* mm. water; all types of breathing; with and without anesthesia.

Pressure in Living Animals in the Horizontal Position. A negative intra-abdominal pressure is not restricted to the epigastric region. With the animal lying on its back the same pressure readings are obtained when the needle is inserted at any point in the anterior belly wall from the ensiform to the symphysis. No intra-abdominal pressure readings are obtainable, with the animal in this position, if the needle be inserted posteriorly or posterolaterally, due to the posterior gravitation of the abdominal viscera.

With the animal lying on its stomach or standing in a normal manner pressure readings can be obtained if the needle be inserted in the epigastric region. The same readings are obtained if the needle is inserted into the abdominal cavity posteriorly at any point along the dorsolumbar spine. No readings are obtainable, however, at any point on the anterior abdominal wall below the epigastric space—again due to gravitation of the abdominal viscera.

Change to the Vertical Position. Change of the animal from the horizontal to the vertical position produces a marked change in the intra-abdominal pressure. The negative pressure in the epigastric region increases as the vertical position is assumed and is associated with a fall in general blood pressure and more or less respiratory embarrassment. The degree of increase is dependent upon the tonus of the abdominal muscles and upon the type of breathing.

The change in intra-abdominal pressure accompanying changes of position is shown in the following experiments. An anesthetized or unanesthetized dog was laid on his back upon an animal board. The needle was inserted through the epigastrium and the pressure noted. The head of the board was slowly elevated until vertical. Either a continuous record or intermittent readings were made.

Examples. An etherized dog with the needle through the epigastrium, whose horizontal reading was $-\frac{10}{16}$* mm. of water, showed a gradual increase of negative pressure as the vertical was approached. At the vertical the pressure was $-\frac{115}{162}$* mm. of water, an increase of over tenfold. At the same time the general blood pressure, as measured by carotid cannula and mercury manometer, fell 22 mm. of mercury; the respirations increased in rate and decreased in depth. In the above it is to be noted that due to the anesthesia there was complete relaxation of the abdominal muscles. (The

* Numerator indicates minimum pressure; denominator maximum pressure (See explanation in text.)

same degree of increase of intra-abdominal pressure is observed if a dead animal is used.)

Using an unanesthetized dog, breathing quietly, the pressure reading in the horizontal position was $-\frac{2}{4}\frac{6}{2}$* mm. of water; in the vertical position the pressure became $-\frac{4}{8}\frac{1}{5}$* mm. of water, an increase of twofold. There was slight respiratory embarrassment. Because of the lack of anesthesia there was incomplete relaxation of the abdominal muscles, and therefore a limited increase of the negative intra-abdominal pressure. When the respirations of an unanesthetized animal were increased in rate and depth, and his muscles taut through fear, there was no increase in the negative intra-abdominal pressure in changing from the horizontal to the vertical position.

When the needle is inserted just above the symphysis pubis, and the pelvis elevated, the same increase in negative intra-abdominal pressure occurs as when the needle is inserted in the epigastrium and the head elevated.

The increase in the negative intra-abdominal pressure when the animal is changed from the horizontal to the vertical position is dependent upon an increase in the size of the abdominal cavity at the point measured. This is accomplished by the sinking of the abdominal viscera, and the degree of downward displacement of the viscera is dependent directly upon the state of the abdominal muscles; if they be completely relaxed the viscera will sink to their lowest level; if the muscles are possessed of a certain amount of tonus the downward gravitation of the viscera will be correspondingly limited.

One of the most instructive examples of the role of the abdominal muscles is found in the experiment of Hill and Barnard. If a tame rabbit be held in the vertical position, head up, the animal will die in a short time of cerebral anemia, due to venous engorgement of the splanchnic area.† If the experiment be tried with a wild rabbit whose abdominal muscles are strongly developed, or if the belly wall of the tame rabbit be supported by a bandage, the animal will not die.

Persistence of Negative Intra-abdominal Pressure after Death. Negative intra-abdominal pressure persists after death. Many readings were made on animals, chiefly dogs, immediately after death and before the onset of rigor mortis. The pressure after death corresponded to the maximum negative pressure of the living animals, 40 mm. of water.

* Numerator indicates minimum pressure; denominator maximum pressure. (See explanation in text.)

† With the etherized animal in the vertical position it can be seen through the unopened peritoneum that a distance of from 7 to 15 cm. separates the superior surface of the liver from the inferior surface of the diaphragm. The normal space is accentuated by the sinking of the viscera which bulge out the lower abdominal walls. This space is an actual abdominal cavity.

Eight dogs, extremely emaciated, that died of inanition due to previous operative procedures, exhibited enormous increases in negative intra-abdominal pressures. These readings, taken before the onset of rigor mortis, ranged from −150 to −270 mm. of water. In these animals there was complete utilization of all omental, mesenteric and capsular fat, with the result that the size of the abdominal cavity was increased. The abdominal walls were tense and contracted; the abdominal contour, scaphoid. When a small opening was made in the anterior abdominal wall a prolonged hissing of inrushing air was heard. This was followed by a gradual relaxation of the abdominal walls and the resumption of the normal abdominal contour.

The appended table is composed of the intra-abdominal pressure readings made upon fifty consecutive cadavers from the mortuary of the Philadelphia General Hospital. The needle, tubing and manometer used in the animal work were employed here. The needle was thrust through the epigastrium with the cadaver in the supine position.

The tabulated cases fall into three groups:*

A, 1 to 19, pathologic increase of negative pressure.

B, 20 to 41, more or less normal negative pressure.

C, 42 to 50, pathologic positive pressure.

From the above cases several interesting facts are noted:

1. Forty-one out of fifty have a negative intra-abdominal pressure.

2. The pathologic increase in the negative pressure noted in Group A is accompanied by extreme emaciation as a common factor.

3. The pathologic positive pressure noted in Group C is accompanied by a decrease in the size of the abdominal cavity due to the presence of ascites, extreme intestinal distention and abdominal tumor.

4. The normal, Group B, includes a stillborn. This is remarkable in that it demonstrates the existence of a negative intra-abdominal pressure before pulmonary respiration has been established.

5. Two infants, one seven and the other nine weeks of age, had negative pressures and the more emaciated infant had the greater negative pressure.

6. Sex, race and age played no part so far as the differences of pressure are concerned.

The Reëstablishment of Negative Intra-abdominal Pressure. The injection of gases into the abdominal cavity obviously effects an increase in the intra-abdominal pressure. That such gases are absorbed from the abdominal cavity has frequently been demon-

* The bodies immediately after death are placed in the mortuary which is refrigerated and maintained at a temperature of 30° to 40° F. No allowance is made in the above cases for rigor mortis or intestinal distention of postmortal origin. This is permissible in that rigor or postmortal distention would, if present, decrease rather than increase the negative intra-abdominal pressure.

RECORD OF THE INTRA-ABDOMINAL PRESSURE IN FIFTY CADAVERS FROM THE MORTUARY OF THE PHILADELPHIA GENERAL HOSPITAL.

No.	Color.	Sex.	Age.	Hours after Death.	Pressure, mm. water.	Remarks.
1	W.	M.	65 yrs.	3	−106	Extreme emaciation, carcinoma
2	W.	F.	67 "	28	− 92	Extreme emaciation
3	W.	M.	63 "	52	− 88	Extreme emaciation
4	W.	M.	60 "	9	− 70	Extreme emaciation
5	W.	M.	76 "	18	− 70	Extreme emaciation
6	W.	M.	42 "	17	− 62	Extreme emaciation, carcinoma
7	W.	M.	68 "	7	− 60	Extreme emaciation
8	W.	M.	60 "	10	− 60	Extreme emaciation
9	W.	M.	72 "	5	− 60	Extreme emaciation, carcinoma
10	W.	F.	75 "	11	− 58	Extreme emaciation, carcinoma
11	W.	F.	48 "	15	− 50	Emaciation
12	W.	M.	60 "	21	− 50	Emaciation
13	W.	M.	40 "	9	− 44	Emaciation, pulmonary tuberculosis
14	W.	F.	84 "	18	− 44	Emaciation, senility
15	W.	M.	9 wks.	72	− 40	Emaciation, inanition
16	B.	M.	47 yrs.	16	− 40	Thin
17	W.	M.	45 "	18	− 34	Thin
18	W.	M.	52 "	24	− 32	Thin
19	W.	M.	60 "	18	− 30	Thin
20	B.	F.	60 "	9	− 20	
21	B.	M.	42 "	6	− 20	
22	W.	F.	60 "	18	− 20	
23	W.	M.	61 "	18	− 18	
24	W.	M.	80 "	16	− 18	
25	W.	M.	48 "	12	− 18	
26	B.	F.	7 wks.	74	− 18	
27	B.	M.	37 yrs.	15	− 16	
28	B.	M.	37 "	9	− 16	
29	B.	F.	54 "	4	− 12	No rigor mortis
30	W.	F.	56 "	4	− 10	No rigor mortis
31	W.	M.	40 "	19	− 10	
32	W.	F.	58 "	20	− 10	
33	B.	F.	55 "	18	− 10	
34	W.	M.	48 "	30	− 10	
35	B.	M.	72 "	41	− 10	Thin, some intestinal distention
36	W.	F.		27	− 8	Stillborn; six months
37	W.	M.	79 "	36	− 8	
38	W.	M.	64 "	5	− 8	No rigor mortis
39	W.	F.	72 "	14	− 6	
40	B.	F.	58 "	8	− 4	Large abdomen, fat.
41	W.	F.	63 "	12	− 2	Very obese
42	W.	M.	72 "	8	+ 4	Some intestinal distention
43	W.	M.	60 "	18	+ 6	Obese, fluid in abdomen and chest
44	B.	M.	72 "	4	+ 10	Obese
45	B.	M.	44 "	43	+ 30	Ascites
46	W.	M.	60 "	14	+ 46	Ascites
47	W.	M.	52 "	16	+ 60	Obese, abdominal tumor
48	B.	M.	24 "	12	+110	Pneumonia, extreme intestinal distention
49	B.	M.	37 "	14	+120	Pneumonia, extreme intestinal distention
50	B.	M.	49 "	16	+150	Pneumonia, extreme intestinal distention

strated by roentgenograms of the abdomen following such clinical procedures as Rubin's[27] test and artificial pneumoperitoneum. It is my belief that absorption of such gases proceeds until there is restoration of a normal negative pressure.

To test the above hypothesis the intra-abdominal pressure was measured before and at intervals after operative opening and closing of the abdomen in 10 dogs. The intra-abdominal pressure before operation was always negative, averaging $-\frac{24}{40}$* mm. of water. Immediately after closure of the abdominal incision the pressure averaged $+\frac{14}{6}$* mm. of water. Six hours later the pressure was approximately atmospheric. Twelve hours after operation the intra-abdominal pressure was slightly negative, $-\frac{4}{18}$* mm. of water. Twenty-four to thirty-six hours usually elapsed before the intra-abdominal pressure attained its average normal level of $-\frac{24}{40}$* mm. of water. If the same experiment were repeated in man I believe reëstablishment of the negative intra-abdominal pressure would be observed.

The time interval necessary for the absorption of different gases, and hence the reëstablishment of negative intra-abdominal pressure, varies with the particular gas present as well as with certain physical and physiologic factors. For instance, the intra-abdominal pressure returns to a normal level more slowly after air or oxygen has been admitted to the abdominal cavity than it does after the admission of carbon dioxide. This was clearly demonstrated by the following experiment:

Four dogs were taken, placed on their backs and a hollow needle plunged through their anterior belly walls in the epigastrium. Connected to the needle by rubber tubing and a T tube were a water manometer and a flask containing, under pressure, the gas to be injected. The normal intra-abdominal pressure was noted. Into two of the dogs carbon dioxide was injected until the intra-abdominal pressures rose to $+\frac{54}{46}$* and $+\frac{62}{58}$* mm. of water. The needle was left in place through the course of these two experiments and readings were taken at frequent intervals. Chart I shows the time necessary for the intra-abdominal pressure to return to approximately its normal level. In both cases the time interval was less than thirty minutes.

Into the other two dogs oxygen was injected until the intra-abdominal pressure rose to $+\frac{30}{20}$* mm. of water. Readings were made at various intervals through the day and at the end of a twenty-four hour period. Between the readings the animals were allowed the freedom of the laboratory. Chart II is a composite curve of the two sets of readings made upon the dogs into which oxygen had been injected. After a period of twenty-four hours the intra-abdominal pressure had approached but did not attain the normal level.

* Numerator indicates minimum pressure; denominator maximum pressure (See explanation in text.)

That a similar slow rate of absorption exists in the human being is confirmed by Rubin's case:[28] Oxygen, 1.5 liters, was injected by his technique into the abdominal cavity of a woman to demon-

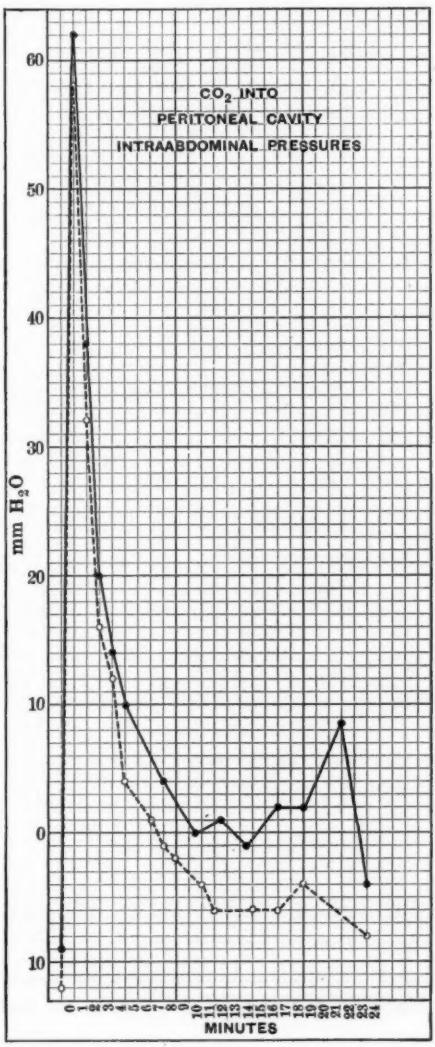

CHART I.—Solid line = minimum pressure, broken line = maximum pressure.

strate the patency of the Fallopian tubes. Subsequent roentgenograms demonstrated the presence of the gas within the abdominal cavity until seventy-two hours after injection.

Conclusions. 1. Direct measurement of the intra-abdominal pressure in living animals proves that the pressure is negative or subatmospheric.

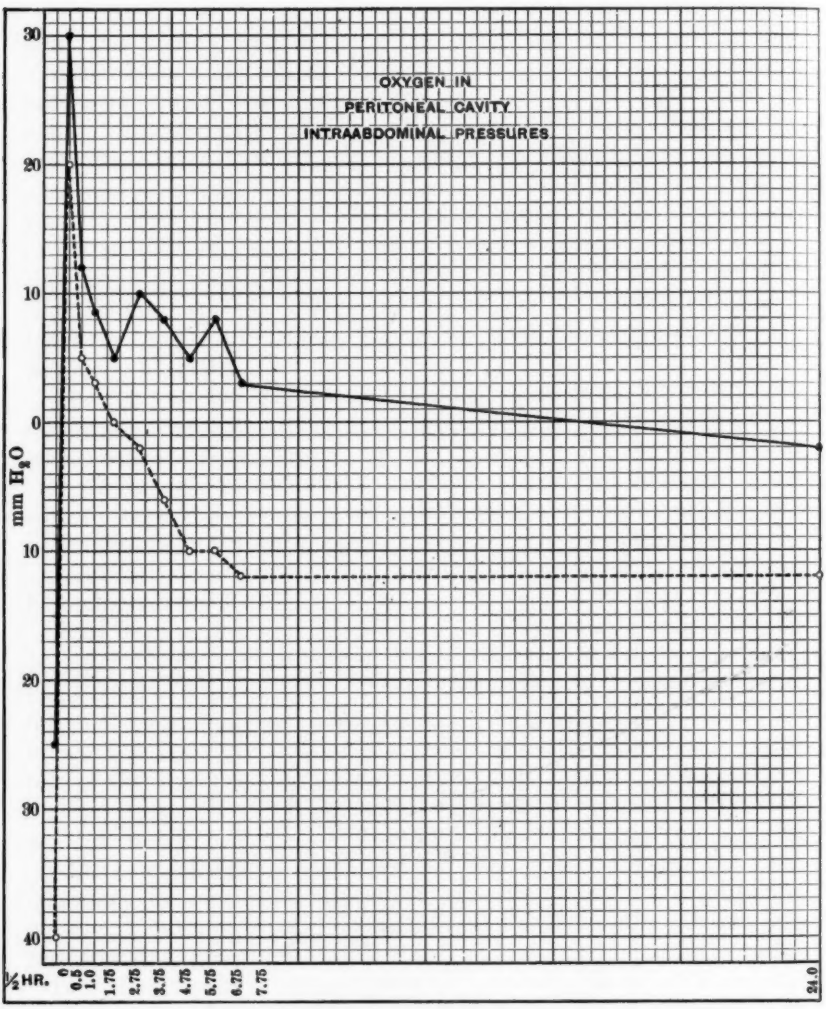

CHART II.—Solid line = minimum pressure, broken line = maximum pressure.

2. Measurement of the intra-abdominal pressure in living and dead animals and cadavers shows that a negative pressure exists before birth, is present during life and persists after death.

3. Changes in the intra-abdominal pressure are due to changes in the size of the abdominal cavity.

4. Alterations in the size of the abdominal cavity are induced by: (*a*) Changes in the rate and depth of respiration; (*b*) tonus of the

abdominal wall; (*c*) changes in the bulk and position of the abdominal viscera.

5. Absorption of gases admitted to the abdominal cavity proceeds until there is reëstablishment of the negative intra-abdominal pressure normal to the individual.

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HEALTH DIAGNOSIS IN CHILDREN.*

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The word health is generally accepted to mean a condition of body free from physical disease. By disease is meant any departure from health presenting marked symptoms. On the basis of the definition of these two terms a child who does not exhibit some one of

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the specific diseases listed in medical textbooks and upon whom no distinct diagnosis of illness has been made is considered well and is treated as such.

Impairment of growth and development may be of a grave nature. Yet if the child does not manifest a clearly defined disorder he is still considered well, although in this realm of pseudo health there often may lie the early stages of practically all the chronic conditions, including tuberculosis.

The training afforded the student in the medical school develops high intelligence regarding disease, but does little to increase his understanding of health. Therefore, later when he enters the health field he falls back upon routine and rationalization which, according to Osler, are the two greatest foes to medical progress.

Unfortunately, when a parent, realizing that the child is below par, insists upon a careful and complete examination for the cause the physician resents any attempt to change his method of approach. The parent does not care about labels but does know something should be done. Practically all that many physicians do in such a situation is to send parent and child home to return when the difficulties have gone far enough to be classified in medical pathology.

For this reason the health problem aside from its end result—disease—is left largely to the mercies of any one who may chance to be interested in it—no man's land—where is found the dietitian, physical educator, social worker, teacher, and others who in a well-organized health plan would be valuable aids and adjuncts.

The victim of this condition of affairs is the growing child and back of it loom sickness and death—a morbidity and mortality that increase with the complexities of modern life.

Much confusion has arisen because the problem, as soon as it is attacked, gives evidence that although medical it is educational and social in its nature. This offers immediate opportunity to the lay worker who is quite right in the essence of his vague feeling that social diagnosis is required. It is largely the fault of our profession not to have made it equally clear that the problems are essentially medical and that those who can deal best with them are physicians with their necessary knowledge of pathology reënforced by training in positive, constructive health diagnosis and preventive medicine.

That this has not been done is all the more remarkable since the intelligent program used for the first year of life is one of the greatest achievements of modern medicine. The infant has been rescued from these negative, inadequate methods still characteristic of our care of the later growing years. For the first and only time a high-grade health intelligence has been exercised and the diagnosis of health as well as of disease is made use of. The infant is weighed and measured and the physician takes pride in his being not only free from disease but up to proper standards of weight, growth, and development.

But after the first year of life our health intelligence fails to function. The child is left more and more to chance and if he survives the contagious diseases and other mishaps of the pre-school period he is admitted to school where, regardless of the degree of his physical unfitness, provided he is not sick, he is expected to meet the requirements for children who are really well.

As yet school organization has been little affected by any serious attempt to meet the health needs of the child. The desirability of doing something in this direction is felt to some degree but the school authorities have gone no farther than to lessen their sense of responsibility by preaching health to pupils who by their own efforts alone are practically helpless. A great wave of printed matter has inundated teachers, affording them general information on many aspects of living and this must be passed on to their charges.

Naturally the dictum "Learning by doing" has influenced the school authorities and this has led to another stage in which the pouring in of health information has been supplemented by health chores and other devices for getting the new material over into the life of the child. Great organizations have capitalized this situation and its possibilities. For example, I have before me the instructions of an organization which has highly-developed machinery for entering thousands of schools and homes. The first attack consists of requiring the child to perform eleven daily chores. By doing these he may expect to become well and strong. The chores range from the simple matters, such as carrying a clean handkerchief, to the more difficult one of having a bowel movement every day although no directions are given for finding and removing causes of constipation. The eleven chores, however, are only the beginning of the process, for directions go on in some forty-five separate pages of printed matter with extensive elaboration through a second, third and fourth series—something of a hygienic *cum laude* cumulation ending with a Phi Beta Kappa which calls for eternal vigilance in such matters as neatness of appearance; keeping surroundings sightly and sanitary; personal control of ventilation and temperature; cheerfulness, straightforwardness, cleanmindedness, doing one thing at a time and the most important first; care for the health of others; playing fair; kind acts; a balanced diet; reading matter held 12 inches from the eyes; proper attention to elimination; deep breathing; sleeping without a pillow; washing hair and scalp!

This bewildering rolling up of hygienic proprieties reminds one of the details of the Mosaic code, only that was not taken all at once. Some years past verses appeared which tell how

> "The Centipede was happy quite
> Until the Frog in fun
> Cried 'Which leg comes after which?'
> He studied so with all his might
> That when he tried to run
> The hundred feet fell in the ditch!"

In an effort to avoid this Scylla another organization has undertaken a Charybdis of simplicity. The rules are reduced to eight. I will take time to speak of only four of the eight—the ones which may, in the form in which they are given, easily lead to as much harm as it is expected they will do good. For example, take this requirement "Sleeping long hours with windows open." We have found in our analysis of health habits that great harm comes from irregularity, especially as regards meals. Long hours of sleep is taken as a recommendation for oversleeping on Saturday and Sunday mornings, the only days when the child is not obliged to hurry off to school, thus bringing breakfast into the middle of the morning and causing a consequent disarrangement of the day's program.

Again, one of the rules calls for drinking as much milk as possible. Such advice is not sound because the using of milk to quench thirst is bad practice, as is also the continuation of a liquid diet after infancy. Another of the commandments is "Drink at least four glasses of water a day." Here again no account is taken of the very common practice of washing food down with water and if the child takes as much as a quart of milk a day eight glasses of liquids is excessive. The last of the list is "A bowel movement every morning." Consequently large numbers of children form the habit of taking physic, suppositories or enemas, every day of their lives in order to secure this result.

To illustrate how far afield such socalled health teaching may go, one of the demonstrators for this same organization was drinking two glasses of ice water before lunch as she did not care for water anyway but found that she could drink it iced and thus she could get the four glasses down.

I do not wish to seem to underrate the importance of adequate health habits but I do wish to urge that more consideration be given to adequate means of bringing them about. The son of a friend delighted his parents by giving the closest attention to the antics of a clown who was employed to make these habits spectacular. This delight was increased by immediate lengthening of the time given to morning teeth cleaning. After a number of days the noise in the bathroom led to observation on the part of the father who found his boy standing on his head and rapping his skull with the tooth brush with many variations but forgetting entirely to put the brush into his mouth.

Protests have been made with reference to these chores and it is only fair to state that the requirements in the case of children who are physically unfit have been modified but as yet no adequate effort has been made to utilize the existing machinery of this great organization in the way of finding out fundamental medical and social causes and seeing to their removal. In the meantime "testimonials" from children are published and given as wide circulation

as has been given those for patent medicines. Here are samples published by the staff of a state public health association. A boy in the fourth grade writes, "My face was pale and white and I started eating cabbage, carrots, radishes, corn, and potatoes, and now I have a good color." The boy goes on to say, "I got into the habit of going to bed at seven o'clock and getting up at six o'clock by wanting to be able to mark my score card. . . . I did my chores twelve weeks and didn't forget a clean handkerchief once. Because I did my chores I got a squire's pin." Another boy—age not given—writes, "I wash my hair with emulsified cocoanut oil at least once a month. If you had done this, Grandpa, you would not have been baldheaded. I am never going to grow old for I take physical exercises daily, and sit in good position that my bones may grow properly." Again, "I had the toothache before I started to do the chores but afterwards I did not." And, "If you eat good food you will be well and strong." It is a girl of eleven who writes, "I adore washing handkerchiefs so I do not mind the fourth chore at all."

The New York Tuberculosis Association very properly states in its Bulletin, "There is no medicine that cures tuberculosis. All medicines advertised as 'cures' are cruel frauds." Yet to tell a child, "Do this and you will be well," is equally cruel. There is no greater fallacy taught under the guise of medical advice. The effect of the chore system as now used is to sanction expectations from certain practices which are entirely out of accord with experience and accurate knowledge. The child asks for health and he is given a medal! This is not honest treatment and amounts to a betrayal of his confidence. One of the end results of such methods is clearly seen in the reaction of the high-school boy or girl who has reached the stage where he decides that all this health activity is "bunk" and he will have nothing to do with it.

His experience with the school physician—an anomalous designation!—only helps to convince him of the truth of his conclusion. He has been through the form of passing in a procession with scores of others before a medical observer who hurriedly notes down such pathologic information as cannot escape him in the small amount of time he can give to each individual. Or he has been sent to a room apart where a slightly longer period is given in an attempt to determine his physical condition by examining him through his clothing. In either instance what is accomplished is only a "screening," to use a term recently suggested by a state medical officer. At the best a few "deviations from the normal" have been put on record but comparatively little has been accomplished in setting the child on the road to health.

We have, then, the problem of the physically unfit child lectured to in school on matters of health. Oftentimes his school program is straining him beyond his strength but cannot be modified even

at the request of the best medical authorities. The health chores are exacted from him which are often misleading in their unjustified promises and usually ill adapted to his real needs. The school physician, usually limited by law to the examination of children with clothes on, screens out an occasional deviation from the normal but when it comes to remedying this abnormal condition both he and physicians connected with the private child-helping organization can only refer the child to the family doctor who has had little health training and who resents interference with his patients.

What is the result of this program as it exists today? Students in the upper grades and even on admission to college show as bad a condition of physical unfitness as students in the lower grades. Improvement in health habits have not kept pace with the complexities of living, so that there has been practically no improvement in the health habits of children during the past fifty years. Nor can improvement be brought about by simply training the intellect or securing a temporary change of health habits by rewards, or by inducing children to follow a fixed number of health rules on the false assurance that by so doing they can become well and strong.

Enough has been said to indicate the outlines of the situation. What is the remedy? The foundation stone lies in the program for the first years of infancy to which reference has already been made. Progress will come in so far as we carry this excellent scheme with proper adaptations throughout the entire period of growth and development. At each stage the first necessity is health diagnosis, which is the essence and body of preventive medicine. Physical unfitness as well as actual disease must be considered and the fundamental causes must be found and removed. When this is done the child becomes free to gain, and he is ready for training in health intelligence and health habits.

We have found that the discovery of causes calls for two types of investigation—the physical-growth examination and the social examination. The causes are more often social than medical but as I have stated the end results of physical unfitness include disease, so that the medical aspect assumes fundamental importance. A study of thousands of these examinations shows that the chief causes of physical unfitness during the growing years are: (1) Physical defects, especially nasopharyngeal obstructions; (2) overfatigue; (3) inadequate home or self control; (4) faulty food and food habits; (5) faulty health habits.

But no program to achieve physical fitness is complete unless it is safeguarded against the tendency, on one hand, to assume that because some particular method brings results in certain instances it offers a panacea for all the ills involved, and, on the other hand, a readiness to use some bianket method—or, to change the figure, to load the gun with a charge which includes all known remedies and means of improvement. Each case of physical unfitness is an

individual problem and should be studied as such but a program which brings into coöperation certain essential forces cannot fail to meet the needs of all types of cases. These essential forces are those of the home, the school, medical agencies and of the child's own interest.

This program has had ample opportunity for successful demonstration. It has been tried out in fourteen leading orphan asylums with the result that in each instance underweight and physical unfitness has been practically eliminated from the children concerned. In several of our larger cities, as Rochester and Indianapolis, a thousand or more children at a time in physical-fitness classes have been brought up to normal standards and have continued in that condition to a remarkable degree. Summer camps working on this program have found the solution for problem cases which had baffled most expert medical care. It may seem strange to refer in a meeting of pediatricians to the results secured in colleges, yet the college student is still a member of the growing period and too often he has been allowed to come to the end of his growing years without having attained the full growth and development nature had intended for him. At Dartmouth, the Massachusetts Institute of Technology, St. Xavier College and elsewhere men have learned to look upon health intelligence as a desirable acquisition. The man who had supposed that he lacked strength for physical training, athletics, high scholastic achievement, has learned to build himself up so that he could hold his own with the best.

What the college man at first fears is a form of pampering himself he soon finds is a means of hardening and he rejoices in health accomplishment which he had supposed was outside his range. The program has had some of its best testing in the training of football teams in the midst of their strenuous activities. The results in these cases have been most satisfactory.

I have made several references to the subject of health intelligence. We have made tests of many groups of teachers, nurses, college men and women with reference to the relationship existing between their actual state of health and their health habits. Practically in every instance those who were in good health had good habits and those who had bad health habits suffered poor health. But health habits are not mere matters of routine. Rather they are the practical aspect of intelligent thinking and doing adapted to the stage of development of the particular individual under consideration.

The first steps must be made by pediatricians in their own practice and in the training of medical students. Given a positive constructive conception of health diagnosis, applied throughout the whole period of growth and development in the same way that it is being carried out during the first year of life, we shall be able to prevent disease, reduce the pathology of later life, and give every child an opportunity to secure higher standards of health.

Summary. Present schemes of health "chores," "teaching health," and so forth are ill adapted to real needs and misleading in the impressions they actually make upon children. Intellectual knowledge has little or no permanent effects on health habits.

The work of the school physician usually amounts to a mere "screening" out of a certain number of "deviations from the normal" without getting at causes or removing them.

"Blanket," "shot gun" and panacea methods lead to waste of time, energy and funds much needed for constructive health work which takes account of actual causes and individual needs.

The basis of a program which deals with the entire period of growth is found in the present expert system of care worked out for the first year of infancy.

Adequate provision for proper growth and development requires constructive health diagnosis which utilizes training in pathology without being overshadowed by it. This calls for adequate physical-growth and social examinations to determining the causes of any failure to realize proper physical development and health.

A study of the results of thousands of these examinations show that the most common causes of physical unfitness are: (1) Physical defects, especially nasopharyngeal obstructions; (2) overfatigue; (3) inadequate home or self control; (4) faulty food and food habits; (5) faulty health habits.

A similar study of health habits indicate that good health is found in those persons who practice good health habits and bad health is the accompaniment of faulty health habits. It is also evident that health habits and the state of health do not improve with advancement in school or college grades. For instance, seniors in the medical school do not show better conditions than appear among college freshmen.

A satisfactory program takes account of this state of affairs and brings into operation the forces of: (1) The interest of the individual; (2) the home; (3) the school or college; (4) medical care, in order to remove causes of physical unfitness, bring the individual to a point where he is free to gain and afford him adequate training in proper health habits.

Applications of this program has practically eliminated underweight and malnutrition from fourteen orphan asylums. It has been put into successful operation in many communities from Labrador to the Hawaiian Islands including cities in which a thousand or more children have been under care at one time with immediate and permanent improvement in weight and physical fitness. In various colleges the program has served to remove a large part of the physical unfitness among freshmen and upper classmen alike, demonstrating its efficiency throughout the whole period of growth and development.

Accurate and scientific methods are as necessary in diagnosing health as in diagnosing disease and the application of this principle is essential if we are to obtain permanent and satisfactory results.

PNEUMOPERICARDIUM FROM RADIUM NECROSIS.

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and
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The presence of air or gas in the pericardium is a rare occurrence. It produces extraordinary physical signs which are so striking and characteristic, that they suggest the nature of the trouble immediately. In 1903 James, in a review of the literature, analyzed 37 cases of spontaneous pneumopericardium and added 1 of his own. Since that time we have found reports of 6 additional cases in the literature. Although in many of these the observers met this condition for the first time, they were able to make a correct diagnosis before autopsy.

In most of the cases reported, there was an accidental communication between the pericardium and some other organ which allowed the passage of air or gas into the pericardial sac. In 5 of the cases, however, no perforation was found to account for the presence of the gas. This perforation was produced in various ways. Paracentesis, stab wounds, or fractures of the ribs or sternum caused this condition in some cases. Infection by a gas bacillus formed a large percentage, and erosion through the esophagus or stomach by an ulcer, cancer or by trauma formed still another large group. Diseases of the neighboring organs, such as empyema or abscess of the lungs, or liver with rupture into the pericardium, have also been reported as causes for this condition.

The physical signs in all the cases are very similar. The normal pericardial dullness is replaced by tympany. In some of the cases there is a shifting relation between this pericardial tympany and the adjacent dullness, with change in position of the patient, due to shifting of the fluid in the pericardial sac. One of the most striking physical signs is a splashing, gurgling sound called the "bruit de moulin," because it resembles the noise made by a waterwheel. This sign was first described by Brichetau in 1844. There is also present in many of the cases reported a loud, metallic tinkling, synchronous with the heart sounds. These noises are so pronounced that they can be heard at a distance from the patient, and in many instances the patients themselves hear them. A succussion splash may also be elicited on shaking the patient.

Gas in the pericardium must be differentiated from hydropneumothorax because in the latter condition succussion may be produced by the action of the heart, and the sounds transmitted to

the precordium. In pneumopericardium, however, the sounds are much louder, are heard best over the heart area, and the characteristic signs over this area are strikingly different from those heard over the chest itself. The changing area of the precordial dullness with change of position also helps the observer to differentiate these two conditions. Gas in the ventricles of the heart or mediastinum may cause the bruit de moulin. A positive diagnosis of pneumopericardium can be made by the characteristic Roentgen ray findings.

Case History. The patient, a peddler, aged fifty years, was admitted to a local hospital in July, 1925, complaining of progressive difficulty in swallowing and regurgitation of food. He stated that five months prior to his admission he began to have difficulty in swallowing, and frequently vomited undigested food and mucus shortly after eating. He also complained of a pressing pain over the lower end of the sternum, and marked loss of weight. These symptoms became progressively worse. On his admission to the hospital, an esophagoscopy and gastrointestinal Roentgen ray examination showed an obstruction at the cardiac end of the stomach. A laparotomy was performed and 30 mg. radium in needles were inserted into a mass at the cardiac end of the stomach for fifty hours. A gastrostomy was also done, but after several weeks the gastrostomy tube was removed and the wound allowed to heal. His general condition, however, did not improve and he was transferred to Montefiore Hospital on October 8, 1925. Several days after his admission he developed a sudden rise of temperature, with substernal pain and tenderness over the lower end of the sternum.

On examination the patient appeared acutely ill. He was cyanotic and dyspneic. The lungs showed dullness at both bases, with areas of bronchovesicular breathing and moist crackling rales. The normal precordial dullness was replaced by a dull tympany which merged with the lung areas. On auscultation, the heart sounds were irregular in rate and had a characteristic metallic, tinkling quality. A peculiar splashing noise, the bruit de moulin or waterwheel sound, accompanied the heart sounds. A succussion splash was obtained on shaking the patient. The pulses were irregular in rate and rhythm and electrocardiograms showed auricular fibrillation. The rest of the physical examination was negative.

A Roentgen ray gastrointestinal examination taken at this time showed the following:

A small defect was seen high up near the cardiac end of the stomach which was diagnosed as carcinoma. On some of the gastric plates the lower portion of the heart and lungs were seen, and air was noted in the pericardial sac. The patient was then reëxamined under fluoroscopic control and showed the following: The barium meal was seen to pass down the esophagus without evi-

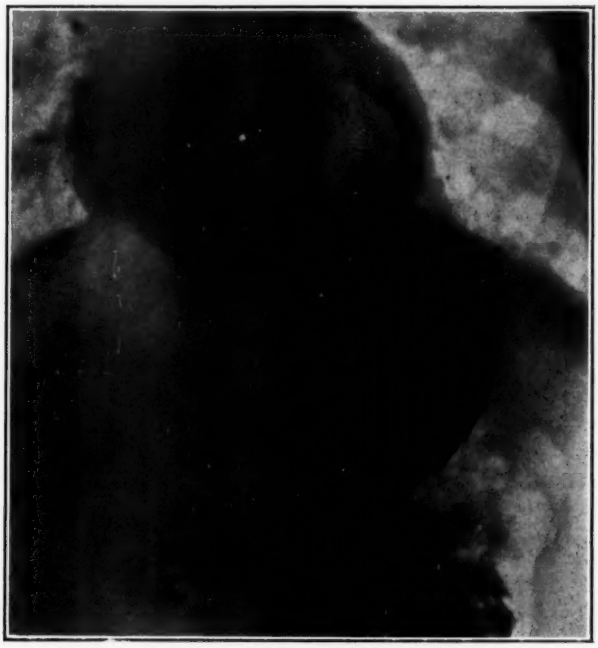

PLATE I.—Demonstrating the air in the pericardial sac and the thickening of the walls.

PLATE II.—Showing barium having entered the pericardial sac with the patient prone.

PLATE III.—Perforation through the pericardium communicating with the stomach.

dence of any obstruction. At the level of the diaphragm some of the meal passed directly into the stomach, while some entered the pericardial sac, causing a marked increase in the cardiac shadow. In a few seconds all the barium passed into the stomach, leaving air in the pericardium. By placing the patient, however, in a slight Trendelenburg position some barium reëntered the pericardial sac.

Plate I. A chest plate taken in the erect position showed the following: The cardiac shadow was composed of two distinct portions: An outer circular bag, consisting of the pericardium, and an inner shadow of the heart. They were separated by a distance varying as much as 1¼ inches. The heart itself was approximately normal in size and shape, but the pericardial sac was baglike and markedly enlarged. Its walls appeared somewhat thickened and were about ⅛ inch thick to almost ½ inch thick in the region of its attachment to the diaphragm. No adhesions were seen.

In the lungs bronchopneumonia at both bases and some infiltrations, pneumonic in type, were present in the right upper lobe. A few small calcified tuberculous lesions were also seen in the left upper lobe.

Plate II. Immediately after the barium meal a film was taken with the patient in a prone position and showed that some of the barium had entered the pericardial sac.

The patient became progressively worse, and died four days after the lesion was demonstrated by Roentgen ray. An autopsy was obtained.

Autopsy. (Performed thirteen hours postmortem, by Dr. D. P. Seecof.) On opening the chest, the pericardial sac is slightly enlarged and cushiony (air-containing). It is thickened and markedly dilated. The epicardium is covered with a peculiar greenish-brown purulent exudate which has but slight tendency toward fibrin deposition. There are some small particles of barium lying free in the pericardial sac. At about the inferior junction of the posterior and left walls of the pericardium there is a circular-shaped opening, measuring 3 cm. in diameter, leading directly into a cavity formed at the junction of the cardiac end of the stomach and the esophagus. The parietal and visceral pericardia present a very peculiar appearance. They are covered with a thick layer of greenish-brown, organizing, fibrinopurulent material, so that the surface markings are completely obliterated. The heart is slightly hypertrophied but there is no disease of its walls or valves. On opening the esophagus there is a large perforation about 3 cm. in diameter near the cardiac orifice of the stomach which takes up the entire anterior lateral wall. The free borders of this opening are sharp, the mucous membranes lining it are thickened, and appear punched out, with practically no attempt at granulation. The free surface of the border is necrotic and greenish-yellow in color.

Microscopic Examination. Sections taken from the wall of the stomach show adenocarcinoma. There is a large amount of fibrosis present. Several sections immediately surrounding the perforation contain the cancer outlines of destroyed tumor tissue.

Anatomic Diagnosis. (*a*) Pneumopericardium with organizing pericarditis, subsequent to fistula formation between cardia of the stomach and pericardial sac.

(*b*) Localized adhesive pericarditis.

(*c*) Adenocarcinoma of the stomach.

Summary. 1. The unusual and striking physical signs encountered in cases of pneumopericardium make a correct diagnosis very simple.

2. This report apparently constitutes the first time that this condition has been produced by radium necrosis, and definitely demonstrated by the presence of barium in the pericardial sac.

CASES REPORTED SINCE JAMES' SUMMARY IN 1903 INCLUDING THREE QUOTED CASES.

Number.	Reporter.	Cause.	Physical signs.	Result.	Autopsy.
1 . .	Cowen, Harrington and Riddell	Suppuration of lung penetrating the pericardium	Tympany; metallic tinkle; Roentgen ray pictures obtained	Recovery	
2 . .	Zwilling	Tuberculous abscess between esophagus and pericardium with perforation into both	Tympany; bruit de moulin, metallic sound synchronous with heart beat. Roentgen ray pictures obtained	Death	Yes
3 . .	Burke	Punctured stab wound	Tympany; metallic sound synchronous with heart beat	Operation with recovery	
4 . .	Lundie	Rupture of tuberculous abscess into pericardium	Tympany over precordium, metallic tinkle synchronous with heart sounds. Bruit de moulin	Recovery	
5 . .	Sarauer	Infection with gas bacillus producing pericarditis	Tympany; metallic tinkle	Recovery	
6 . .	Love	Etiology not determined	Tympany; metallic click heard at a distance	Recovery	
7 . .	Gottesman and Bendick	Radium necrosis secondary to carcinoma of cardiac end of stomach	Tympany; succussion splash, metallic tinkle synchronous with heart sounds; bruit de moulin; Roentgen ray pictures obtained	Death	Yes

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EPHEDRIN IN ASTHMA.*

A Clinical Report.

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Observation of the clinical effects of ephedrin has convinced me that this drug is an important addition to our means of relieving the suffering of asthmatic patients. These few data are published in the hope of arousing the interest of others who treat asthma so that they may investigate for themselves the effects of the drug and thus expedite what I believe will be its eventual widespread employment in this syndrome. A supply can be obtained from the Department of Pharmacology, Peking Union Medical College, Peking, China.

Ephedrin is an alkaloid, the active principle of a plant, Ma Huang or Ephedra vulgaris, var. helvetica, which grows abundantly in China. For many centuries the herb has been used there empirically for the relief of asthma, but it remained for workers in the Peking Union Medical College to study scientifically the effects of its active principle upon animals. Their published results[1, 2, 3] show that the physiologic effects of the drug resemble closely those of epinephrin and are all comparable to those of stimulation of the sympathetic nerve.

Miller[4] has published the results of eighty-four clinical experiments apparently based upon the administration of single doses of ephedrin to patients suffering from a variety of diseases, including a few cases of asthma. Favorable results are noted in his own cases as well as in a series of cases of asthma reported to him by others, and Miller believes that ephedrin will be found to be useful in the treatment of asthma, of acute circulatory depression and in the management of certain congestive nasal conditions.

In the present report are shown in tabular form some results of the administration of ephedrin to asthmatic patients, also some

* Read before The Society for the Study of Asthma and Allied Conditions, at Albany, April 2, 1926.

EFFECTS OF EPHEDRIN UPON ASTHMATIC PATIENTS.

No.	Name.	Sex.	Age.	Skin reaction to proteins.	Type of asthma.	Duration of asthmatic state.	Dose employed, mg.	Duration of relief.	Other effects, complications, remarks.
1	L. N.	F.	63	Negative	Severe; remittent	3 yrs.	30	5 to 8 hours	No unpleasant effects from 35 mg., but 50 mg. causes palpitation and tremor. For past 3 weeks, while taking 6-hourly doses has been asthma-free for first time in two years. Without ephedrin, requires 2 to 4 doses of epinephrin daily. Blood pressure not affected. Urine normal after 3 weeks' use of ephedrin.
2	E. M.	F.	47	Negative	Severe; remittent	13 mos.	50	4 to 5 hours	Blood pressure not affected. Myocarditis and extra systoles apparently not affected. Four-hourly doses of ephedrin keep her asthma-free. Without it she suffers from asthma despite 2 to 5 daily doses of epinephrin. Normal urine after 3 weeks' use of ephedrin.
3	E. R.	M.	54	Negative	Severe; intermittent	3 yrs.	50	4 hours	See special report below. Blood pressure (145/100) not affected in 6 observations before and after ephedrin. Asthma-free while taking 2 daily doses of ephedrin. Without it, has required 4 to 6 doses of epinephrin daily.
4	M. K.	M.	45	Feathers; mouse hair	Severe; intermittent	15 yrs.	50	No relief	Headache and palpitation; has improved under autogenous vaccine treatment, guided by skin tests with same, but requires 4 to 6 doses of epinephrin daily; blood pressure (120/85) is not affected by ephedrin.
5	S. S.	F.	44	Negative	Severe; intermittent	10 yrs.	50	No relief	Headache, tremor and nausea.
6	F. S.	F.	29	Wheat, egg, orris, feathers	Severe; intermittent	10 mos.	30 to 50	No relief	Headache, tremor and nausea; slight increase in blood pressure.
7	J. K.	M.	73	Negative	Severe; intermittent	4 yrs.	30 to 50	12 hours	Bladder irritation; pollakiuria, sufficient to require discontinuance of the drug although relief from asthma was complete for 12 hours on 2 occasions; usually requires 2 to 4 doses of epinephrin nightly; hypertension, not increased by ephedrin.
8	L. G.	M.	57	Negative	Mild; intermittent	15 yrs.	50	6 to 12 hours	For years has required 4 to 8 inhalations daily of "asthma powder" smoke; for 3 weeks past has been practically asthma-free while taking ephedrin twice daily as a preventative.
9	J. F.	M.	2½	Silk and many foods	Severe; intermittent	2 yrs.	7	12 hours	See special report, below.
						6 yrs.	13	12 hours	Asthma almost continuous for a month before taking

9	J. F.	M.	2½	Silk and many foods	Severe; intermittent	2 yrs.	7	12 hours	See special report, below.
10	P. H.	M.	10	Air-borne and food proteins	Severe; remittent	6 yrs.	13	12 hours or more	Asthma almost continuous for a month before taking ephedrin, since which has been asthma-free for two weeks.
11	R. C.	M.	36	Negative	Mild; intermittent	4 yrs.	50	6 to 12 hours	Slight sweating of head, lasting a few minutes; is asthma-free while taking ephedrin twice daily; blood pressure (120/90) not affected.
12	M. H.	F.	54	No tests	Mild; intermittent	7 yrs.	50	6 to 48 hours	Slight tremor; clinical experience makes it appear probable that she is sensitive to orris, feathers and pork; blood pressure, normal, raised 10 to 15 mm.
13	C. W.	M.	46	Negative	Severe; seasonal	9 yrs.	50 to 100	6 to 8 hours	Mild sweating lasting an hour or more; insomnia makes use of drug impracticable; though asthmatic only in summer, skin gives negative reactions to all pollen tests and summer foods used by patient.
14	F. K.	F.	55	No tests	Moderately severe; intermittent	2 yrs.	50	6 to 12 hours	Two attacks relieved in 20 minutes; has been accustomed to burn asthma powder two or three times daily; hypertension and nephritis.
15	M. G.	F.	53	Feathers; rabbit dander	Moderately severe	2 yrs.	50	6 to 12 hours	Three attacks treated; each relieved in 30 minutes; for past week has been asthma-free while taking 2 doses daily.
16	M. J.	F.	28	Feathers	Severe; remittent	1 year	50	12 hours	Continues to live in contact with feathers in spite of instructions; on four occasions while suffering severely, took ephedrin and obtained relief lasting 12 hours.
17	E. H.	F.	40	Feathers; mouse hair	Moderately severe	9 mos.	?	4 hours	Partial relief after each of 5 doses of Ma Huang infusion in an amount said to contain 50 mg. ephedrin; later, removal of infected tonsils was followed by relief from asthma for 4 weeks only.
18	M. B.	F.	50	Negative	Mild; in cool weather only	20 yrs.	50	?	Relief in 20 minutes; no recurrence of asthma for 5 days; usual interval between attacks has been 2 or 3 days.
19	G. C.	M.	53	Feathers	Severe; remittent	9 yrs.	50	6 to 24(?) hours	Has taken 1700 injections of epinephrin during the past year; see special report below.
20	E. G.	M.	36	Feathers; many foods	Mild; intermittent	1 yr.	50	12 hours	No effects noted other than relief of symptoms; asthma-free for 3 weeks while taking 1 or 2 doses daily; previously was having 1 to 3 mild attacks daily.

clinical notes in a few individual cases. By "asthma" and "asthmatic" I mean to refer solely to the symptom of bronchospasm, due to what is commonly known but not well understood as allergy, or else to infection.

Inspection of these tables will show that in the large majority of instances ephedrin relieved the asthmatic paroxysm or kept the patient free from discomfort during the period of its use as a preventative. Not always is it effectual, however, nor is its administration practicable in every case, even though the asthmatic symptoms be relieved. (See Case No. 7 in table.) In some instances, not only was it ineffectual, but it also produced unpleasant effects in ordinary doses. (Cases V and VI). Whether the long continued administration of ephedrin will cause any untoward effects is not yet known, but there is no evidence before me to lead to the anticipation of them. Meantime in two cases of almost continuously severe suffering with asthma (Nos. I and II) of long duration and apparently hopeless, there has been entire relief while taking no other remedy than ephedrin. The drug was given for weeks at a time and no ill-effects have been discovered.

Its effect upon blood pressure has been either absent or inconsiderable in all cases tested among asthmatic patients, but in a sixteen year old girl with giant urticaria and hypertension, without demonstrable nephritis, the administration of 50 mgm. of ephedrin was followed by a transitory rise in arterial tension from 160/100 mm. to 200/150 mm. Its taste is slightly bitter.

Administration of the drug hypodermically is feasible and naturally more rapid in its effect, but the uselessness of epinephrin when given by mouth has been a matter of regret so often and for so long a time that I welcomed the advent of a substitute which might relieve the asthmatic paroxysm without the necessity for a subcutaneous injection. In all cases here reported the drug was given by mouth.

The dose employed has been usually 50 mgm. to adults. If ineffectual, it was increased; if it caused tremor, palpitation or other unpleasant symptoms, it was reduced. Children received doses in proportion to their size and age. In a few cases the drug was administered, for convenience's sake in capsules, but usually in aqueous solution where 1 minim contained 2 mg. of the drug. This approximates a 3 per cent solution, and is of a concentration suitable for use as a nasal spray as well, and when so used is found to shrink the nasal mucous membrane if swollen.[5]

When relief from asthma occurs after the ingestion of ephedrin, it appears regularly in about thirty minutes, and as will be seen in the table, it lasts from four to twenty-four hours; very much longer, as a rule, than is the case with epinephrin.

Subjoined are special clinical notes in 2 cases and a comparison of the effects of epinephrin and those of ephedrin in 3 others.

CASE XIX.—G. C., aged fifty-three years, required four to eight injections of epinephrin daily for a year. While taking ephedrin there was a diminution of the sphincter vesicæ reflex so that on one occasion the patient "forgot" to void urine for more than twenty-four hours, but he then passed a large amount of normal urine without trouble.

After relief by ephedrin, sensitization to feathers was discovered. Since then, contact with them has been avoided, and the patient is now free from asthma and drugs.

CASE IX.—J. F., aged two and a half years, healthy except for a daily attack of vomiting and severe asthmatic paroxysms lasting several days and occurring at intervals of a week or ten days. Positive skin reactions to proteins of feathers, egg and many other foods were obtained. During the course of the skin tests, and after the discontinuance of eggs had been followed by a cessation of vomiting, a severe attack of asthma occurred. Inhalation of smoke from burning "asthma powder" gave partial relief and was continued for the best part of twenty-four hours. At nine o'clock in the evening, while having severe asthma in a small room filled with the fumes of the burning powder, a dose of 14 mg. of ephedrin was given to the child and he was removed to a room in which there was no smoke. In thirty minutes the dyspnea and wheezing ceased, the child fell asleep, slept ten hours and awoke free from asthma, which has not recurred.

Comparison of Effects of Ephedrin and Epinephrin. CASE III.—Dr. E. R. had severe intermittent asthma of three years' duration; has been receiving autogenous vaccine treatment guided by the reactions to intradermal tests with the same, and is now asthma free, requiring no drugs. Was still having severe paroxysms when ephedrin was first administered.

EFFECT OF:

Ephedrin by Mouth.	*Epinephrin Subcutaneously.*
Complete relief in forty minutes.	Partial relief in fifteen minutes.
Complete relief lasts four hours.	Partial relief lasts four hours.
Dryness of mouth and throat.	No dryness of mouth or throat.
No tremor.	Marked tremor.
Profuse expectoration begins in fifteen minutes and lasts fifteen or twenty minutes, after which bronchospasm is relieved.	Sequence of expectoration and relief are the same.
Blood pressure (145/100), not affected in one hour; 6 observations.	Blood pressure not observed.

CASE I.—L. N., aged sixty-three years, has had severe, almost continuous asthma for two and a half years past. Has had much treatment by vaccines, radiotherapy, Dowling pack, and so forth without relief. Gives negative skin reactions to all proteins tested.

EFFECT OF:

Ephedrin by Mouth.	*Epinephrin Subcutaneously.*
Complete relief in thirty minutes.	Complete relief in ten minutes.
Relief lasts six to eight hours.	Relief lasts two to six hours.
No tremor unless overdosed.	Marked tremor from dose necessary to relieve bronchospasm.
No palpitation.	Moderate palpitation.
Blood pressure before, 120/80; one hour after, 115/80.	Blood pressure not observed.

CASE II.—E. M., aged forty-six years, has had severe, almost continuous asthma for the past thirteen months, with pansinusitis, atrophic rhinitis; myocarditis; extrasystoles. Has had vaccine treatment, radiotherapy, special rhinologic treatment, including Dowling pack and so forth, without relief. Protein skin reactions all negative.

EFFECT OF:

Ephedrin by Mouth.	*Epinephrin Subcutaneously.*
Complete relief in about thirty minutes.	Partial relief in twenty minutes.
Relief lasts four to six hours.	Relief lasts two to three hours.
No tremor.	Slight tremor.
No palpitation.	Palpitation.
No disagreeable effects.	Frequently causes extrasystoles and headache.
Nausea if overdosed.	No nausea.

Conclusions. Ephedrin, administered by mouth to a series of 20 patients, suffering from asthma, has given relief to all but 3 and is an important substitute for epinephrin as a palliative remedy. In certain respects and in certain cases the newer drug is to be preferred.

In certain asthmatic patients for whom no means of permanent relief has been found, the drug has been used in regularly continued dosage with the result of keeping them asthma-free during the period of its administration.

Its advantages over epinephrin include: (1) The fact that it is effectual when given by mouth; (2) the fact that its effects are more prolonged than those of epinephrin; (3) the absence, in most cases, of tremor and palpitation as by-effects of doses sufficient to relieve bronchospasm.

Among its disadvantages as compared with epinephrin are: (1) Its occasional failure to relieve asthmatic symptoms where the older drug does relieve. (2) By-effects, occasionally met with, which then render its use impracticable even though it relieve the bronchospasm. (It is possible that these ill-effects may be nullified by proper means.) (3) When given by mouth, its effects are, of course, less rapidly produced than are those of epinephrin given hypodermically. Ephedrin, however, may also be given subcutaneously. (4) Delay in obtaining ephedrin is unavoidable at present.

A field for the use of ephedrin appears to lie in its employment as often as is necessary to prevent the occurrence of paroxysms in asthmatic patients that are awaiting the completion of skin tests, courses of vaccine administration, rhinologic treatment, radiotherapy or other methods from which more permanent benefit is hoped. When effectual, its use in these preventative doses has been more satisfactory than the treatment of paroxysms by injections of epinephrin.

Whether the long-continued administration of this drug to particular patients will prove to be harmful to them or not, is not known at present.

Through the courtesy of Prof. Bernard E. Read of the Department of Pharmacology, Peking Union Medical College, I am enabled to append a bibliography of ephedrin as follows:

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THE CYANOSIS OF DEMENTIA PRAECOX

A Study of the Gas Relationships of the Blood

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With Clinical Observations

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The cyanosis of dementia praecox is a clinical sign observed since the earliest recognition and classification of this psychotic condition. Kraepelin[1] mentions it, as does Bleuler,[2] as a usual bodily symptom, and Cornell[3] has even attributed to it a frequency of 90 per cent in the catatonic forms of dementia praecox. The literature, however, furnishes no record of any direct examination of the blood. Indeed the difficulty of the technique of collection of samples and the unsatisfactory results of gas analyses upon small quantities of blood have limited all scientific investigations of the blood gases in man. The data published previous to 1918 have been upon venous blood, with the exception of a few observations by Hurter[4] upon arterial blood in 1912. Stadie,[5] in 1918, developed the technique of arterial puncture at the Rockefeller Institute, thereby enabling direct analyses of arterial as well as venous blood to be made. With the completion of the method by Van Slyke and Neill,[6] for the determination of gases in small quantities of blood by vacuum extraction, it became possible to obtain a highly quantitative and accurate estimation of the gas relationships in the blood.

In the present investigation the arterial punctures were performed as outlined by Stadie, and the venous punctures were performed without tourniquet to avoid stasis and possible consequent alteration of the gas relationships. In over forty arterial punctures there is no record of untoward consequences.

A group of 16 subjects was selected. Fourteen of these were young male dementia praecox patients; 2 were young male individuals who served as controls. The degree of cyanosis was the criterion for selection of the patients. Only those cases were included who were ambulant, under forty years of age and whose histories were negative in respect to tuberculosis and other debilitating conditions. The average age was twenty-six years, the youngest being sixteen and the oldest thirty-nine years. The clinical findings are presented in the following tables.

Clinical Signs of Cyanosis. Table I represents the degree and extent of cyanosis. Of the 14 patients, 8 exhibited the extreme degree of cyanosis, while 6 were grouped as moderate. In the large majority the upper extremities were more extensively involved than were other parts of the body, the lower extremities, ears and nose following in the order given.

Color. The cyanotic areas of the extremities did not present exactly the color which the term "cyanosis" implies, that is, dark blue, but the appearance was rather that of reddish-blue. This was true irrespective of the extent or location of the cyanosis. Furthermore, the color was uniformly distributed, not mottled. As it progressed proximally it shaded off gradually into the normal color of the skin. There was no appreciable difference in the color of the homologous parts of the body; that is, the same condition existed in the right hand or foot, as existed in the left hand or foot. Likewise, the color of the upper extremities was the same as that of the lower extremities. The ears and nose, however, were usually of a reddish hue and lacked the bluish tinge seen in the limbs.

Extent. Homologous parts were similarly affected in point of extent. In no case was there any marked difference. In 11 cases at least the entire hand was involved, whereas in 3 cases the terminal phalanges alone participated. The feet were less involved; in only 1 case was there cyanosis of the entire foot; in 5 cases the cyanosis was limited to the toes and in 8 the condition extended approximately to the highest point of the instep. When the ears were involved the helix and lobule were cyanotic. The nose was less often involved. Other parts of the body, lips, cheeks or torso did not reveal any cyanosis.

Temperature. The patients were kept in a room heated to about 70° F. for at least three hours before examination. Wherever there was cyanosis the parts felt cold.

Moisture. The affected areas were damp and oily. Noncyanotic parts did not show these qualities.

Pressure, as by the finger, blanched the part and the cyanosis returned quickly with the release of pressure. Raising the hands as high as possible above the heart level caused a slight diminution in the intensity only when the position was maintained for a relatively long period.

TABLE I.—CYANOSIS.

Number.	Name.	Degree of cyanosis.	Color.	Extent.		Ears.	Nose.
				Upper extremities.	Lower extremities.		
1	Sk.	Extreme	Reddish-blue	Entire hand	Toes only	Mild	Absent
2	Ht.	Extreme	"	Entire hand	Toes only	Moderate	Absent
3	Kn.	Extreme	"	Hand and one-third forearm	To instep	Moderate	Moderate
4	Kph.	Moderate	"	Entire hand	To instep	Moderate	Moderate
5	Rmn.	Extreme	"	Hand and one-third forearm	To instep	Moderate	Absent
6	Rn.	Extreme	"	Hand and one-third forearm	Entire foot	Extreme	Absent
7	Tn.	Moderate	"	Entire hand	To instep	Moderate	Absent
8	Pk.	Extreme	"	Terminal phalanges	Toes only	Mild	Absent
9	Ar.	Extreme	"	Hand and one-third forearm	To instep	Moderate	Absent
10	Bc.	Extreme	"	Entire hand	To instep	Moderate	Absent
11	Mz.	Moderate	"	Hand and one-third forearm	To instep	Moderate	Moderate
12	Mkr.	Moderate	"	Entire hand	To instep	Absent	Absent
13	Lg.	Moderate	"	Terminal phalanges only	Toes only	Moderate	Absent
14	Ta.	Moderate	"	Fingers only	Toes only	Moderate	Absent

TABLE II*a*.—CIRCULATORY SYSTEM (DEMENTIA PRAECOX).

No.	Name.	Age.	Weight.	Blood pressure.		Pulse. Pressure.	Heart rate.			Rate of increase due to exercise.
				Systolic.	Diastolic.		At rest.	After exercise.	2 min. after exercise.	
1	Sk.	33	92	104	64	40	60	66	60	6
2	Ht.	29	106	94	68	16	60	76	66	10
3	Kn.	24	108	98	70	28	90	130	105	40
4	Kpn.	17	111	118	70	48	78	120	96	42
5	Rmn.	26	122	102	55	46	60	78	60	18
6	Rn.	30	110	104	80	24	100	122	98	22
7	Tn.	18	118	108	70	38	76	98	76	22
8	Pk.	19	117	96	60	36	80	88	80	8
9	Ar.	25	120	82	50	32	44	58	42	14
10	Bc.	27	100	89	58	31	62	88	60	26
11	Mz.	28	125	88	60	28	44	62	46	18
12	Mkr.	16	137	102	58	44	98	98	100	0
13	Lg.	30	108	110	58	52	80	94	76	14
14	Ta.	39	103	118	86	32	70	92	80	22
Average		26	113	101	65	36	72	91	75	18

TABLE II*b*.—CIRCULATORY SYSTEM (CONTROL CASES).

No.	Name.	Age.	Weight.	Blood pressure.		Pulse Pressure.	Heart rate.			Rate of increase. due to exercise.
				Systolic.	Diastolic.		At rest.	After exercise.	2 min. after exercise.	
1	Dr. Sh.	26	170	116	76	50	74	130	82	56
2	Dr. Lb.	25	140	118	70	48	82	132	84	50
3	Dr. Ds.	30	155	114	70	44	70	138	70	68
4	Dr. Mr.	25	128	116	74	44	72	120	70	48
5	Dr. He.	30	130	120	66	54	70	132	62	62
Average		27	145	117	71	48	74	130	74	57

TABLE III.—LUNGS.

No.	Name.	History.	Physical examination.	Roentgen ray findings.	Sputum tubercle bacilli.	Temperature range, degrees.*
1	Sk.	Negative	Negative	Negative	Not obtainable	98.0– 98.6
2	Ht.	"	Negative	Old healed tuberculosis	Negative	98.2–100.2
3	Kn.	"	Negative	Tuberculosis, not acute	Negative	98.4– 99.2
4	Kpn.	"	Negative	Negative	Negative	98.0– 99.6
5	Rmn.	"	Negative	Negative	Negative	98.0– 99.2
6	Rn.	"	Suggestion	Not obtainable	Not obtainable	98.0– 99.4
7	Th.	"	Negative	Suspicious of tuberculosis	Negative	98.2– 99.4
8	Pk.	"	Negative	Negative	Negative	98.0– 99.6
9	Ar.	"	Negative	Active tuberculosis	Negative	98.0– 99.2
10	Bc.	"	Mild subacute bronchitis	Incipient tuberculosis (?)	Negative	98.0– 99.8
11	Mz.	"	Negative	Subacute tuberculosis	Negative	98.0–100.8
12	Mkr.	"Asthma"	Upper left chest moist rales	Negative	Negative	98.4–102.4
13	Lg.	Negative	Negative	Negative	Negative	98.2–100.8
14	Ta.	Negative	Negative	Active tuberculosis	Not obtainable	98.0– 99.4

* Per rectum taken for one week three times a day.

TABLE IV.

Case.	Oxygen capacity (A), vol. per cent.	Oxygen content of arterial blood (B), vol. per cent.	Percentage saturation of arterial blood B-A x 100, per cent.	Arterial oxygen unsaturation (A-B), vol. per cent.	Oxygen content of venous blood (C), vol. per cent.	Venous oxygen unsaturation (A-C), vol. per cent.	Mean capillary unsaturation $\frac{(A\text{-}C)+(A\text{-}B)}{2}$, vol. per cent.	Oxygen consumption (B-C), vol. per cent.	Carbon dioxide content of arterial blood, vol. per cent.	Carbon dioxide content of venous blood, vol. per cent.	Temperature.	Pulse rate.	Respiratory rate.	Red blood cell count, per million. Arterial.	Red blood cell count, per million. Venous.	Red blood cell count, per million. Capillary.	Hemoglobin in gms.
1–Sk.	19.82	18.40	92.9	1.42	8.90	10.92	6.17	9.50	49.17	51.4	99.4	96	24	5.52	..	5.100	15.1
2–Ht.	20.49	17.41	84.9	3.08	7.38	13.11	8.10	10.03	52.63	55.83	99.0	108	24	5.44	5.52	5.600	15.0
3–Kn.	18.85	17.55	93.1	1.30	11.01	7.84	4.57	6.74	44.51	51.17	99.0	88	24	5.20	5.36	5.015	13.6
4–Kpn.	19.39	17.60	91.1	1.79	7.64	11.73	6.76	9.96	51.82	52.28	98.6	60	18	4.80	5.24	4.605	16.8
5–Rmn.	22.06	20.24	91.8	1.82	13.50	8.56	5.19	6.74	48.52	58.81	98.0	88	20	5.00	5.40	5.710	18.5
6–Rn.	20.30	18.60	91.6	1.70	11.17	9.13	5.41	7.43	52.80	59.40	98.6	88	20	5.20	5.80	4.950	15.8
7–Tn.	18.22	17.79	97.6	0.43	11.54	6.68	3.55	6.25	52.40	55.30	98.6	92	22	..	..	6.400	13.3
8–Pk.	16.30	13.43	82.4	2.87	4.48	11.82	7.35	8.95	46.86	55.11	98.4	72	18	4.48	5.12	5.655	12.2
9–Ar.	18.46	17.41	94.3	1.05	4.57	13.89	7.47	12.94	50.67	58.34	98.0	64	20	5.32	5.68	4.890	13.3
10–Bo.	23.50	22.50	95.7	1.00	9.48	14.02	7.51	13.02	50.50	60.69	98.4	70	19	..	..	4.795	17.8
11–Mz.	22.12	17.79	88.4	2.33	9.94	10.18	6.25	7.85	49.59	56.40	100.0	67	28	..	..	5.200	16.4
12–Mkr.	22.87	19.21	84.0	3.66	10.79	12.08	7.87	8.42	52.65	58.34	..	..	..	4.80	5.20	5.100	15.0
13–Lg.	22.00	18.14	84.2	3.86	14.20	7.80	5.83	3.94	49.22	53.92	..	..	..	..	..	5.350	16.7
14–Ta.	20.14	17.78	88.2	2.36	9.72	10.42	6.39	8.06	50.31	55.49	..	..	..	..	..	5.325	15.7
15–Fl.	19.45	18.98	97.6	0.47	8.27	11.18	5.82	10.71	47.71	57.82	..	..	..	4.80	5.32	..	15.6
16–Fn.	21.97	20.71	94.2	1.26	6.84	15.13	6.78	13.87	47.39	60.29	..	..	..	..	..	4.980	15.9

Circulatory System. *Heart.* The histories of the cardiovascular system were negative in all cases, there being no real or alleged (hypochondriacal) disturbance.

Inspection, palpation, percussion and auscultation gave negative results in all cases but one (Case 12), in which the heart was enlarged downward and outward and was well compensated. This patient was "asthmatic." Apart from this exception, no endo-, myo- or pericardial changes were found.

Table II*a* gives the findings in each case in respect to blood pressure and heart rate before and after exercise.

Tests of the functional capacity of the heart gave some interesting results. A few explanatory remarks at this point are necessary regarding the general condition and activities of the patients included in this study. All of them were nonworkers who sat about the ward all day long, assisting very little in their own personal care. On the whole, theirs was a vegetative existence. Such a state of affairs calls for a very low output of energy and one would, therefore, expect that a sudden vigorous activity would give rise to an exaggerated compensatory response, such as one would not expect from a heart accustomed to meet the demands of a more normal type of existence.

The patients were exercised by running and hopping about for a period of two minutes. All were subjected to the same conditions. For comparison 5 healthy adults were chosen (Table II*b*). It will be seen that the dementia praecox patients showed distinctly less increase of pulse rate and had lower blood and pulse pressures.

Peripheral Arteries. Palpation of the radial arteries gave the impression in all but 2 cases (Cases 11 and 12) that they were definitely of smaller diameter than the average. No difficulty was experienced in the sense that they were anomalously situated, but often because of the feeble force of the blood stream they were hard to trace. Since the walls were soft and so easily compressed, care had to be exercised in arriving at a fair estimation of the relative size of the vessels.

The urine was examined in all cases, but because of the general negative findings the results have not been tabulated. In 3 cases (Cases 6, 10 and 12) a small quantity of albumin appeared on one occasion; subsequent findings were negative.

Pulmonary System. Special attention was paid to the occurrence of tuberculosis, since that condition is known to be so prevalent in cases of dementia praecox. A careful review of the histories revealed nothing suggestive of tuberculosis. On physical examination (necessarily difficult in uncoöperative patients) we found, however, one suggestive case (Case 6) and a second (Case 10) with subacute bronchitis. It was impossible to take a Roentgen ray picture of the first patient and the second was considered by the roentgenologist to be probably in an incipient stage of tuberculosis.

As Table III shows, tuberculosis in one stage or another was found by the roentgenograph in 6 of the 13 cases examined; 6 were negative and 1 was recorded as "suspicious." Sputum examination in 11 cases in which it could be done was reported negative. In 4 cases (Cases 2, 11, 12 and 13) the temperature occasionally went above 100° F. Two cases were considered from Roentgen ray evidence to be actively tuberculous (Cases 9 and 14); clinical examination, including the temperature, was, however, negative in these cases. In fact, apart from the roentgenograph, there was not a single case of undoubted tuberculosis, which means, in other words, that we were not handling, at least, any severe cases.

The association of low arterial tension with pulmonary tuberculosis has often been observed.

Laboratory Procedure. The vacuum extraction method of blood analysis in its most recent form as outlined by Van Slyke and Neill[6] was followed. The blood samples were collected over mercury, as described by Austin, Cullen *et al.*[7] Instead of fitting the outlet of the blood collection tube with rubber tubing and pinchcock, two-way stopcocks were fused to the neck. One outlet of the stopcock was then fitted with a small piece of rubber tubing; the other was used as a waste outlet. This afforded a greater control of the blood flow and insured an absolutely air-tight closing. The blood was drawn under oil in a 20-cc. Luer syringe, the needle removed and the syringe immediately inserted into the rubber tubing.* By opening the stopcock and lowering the mercury reservoir, the blood was drawn into the collection tube. The mercury reservoir was then raised and a small quantity of blood ejected. Since all the glass parts coming in contact with the blood had been coated with a 0.2 per cent solution of neutral potassium oxalate which had been aërated to dryness, there was no danger of clotting.

This method has been found superior to collection under oil, as there is no possible opportunity for diffusion of gases, particularly carbon dioxide, and the sample can be thoroughly mixed without danger of introducing foreign matter.† Furthermore, the keeping quality of the blood is insured for a period of hours in the refrigerator, should this be necessary. All determinations were done in duplicate. The samples were uniformly collected at least three hours after breakfast. The subjects were at rest, being seated quietly for at least one hour before the punctures. Temperature, pulse and respiration records were taken one-half hour before the punctures. Analyses were made immediately after the punctures, as were the red blood cell counts on arterial and venous blood. The counts were made by Miss Anna Steffens, of

* We are indebted to Dr. Carl C. Binger of the Rockefeller Institute for his kindness in demonstrating the arterial puncture and advising us regarding the technique of collecting and handling specimens.

† The method has been described in detail by Dr. Hastings.

the Psychiatric Institute. The capillary red blood cell count was made by Dr. Walter Sanford, of the Manhattan State Hospital, from one to three days later.

The gas relationships are given in Table IV. The total oxygen capacity (Column 2) was determined by saturating a portion of the arterial blood with oxygen in a tonometer and determining the total oxygen that would combine with the hemoglobin in 100 cc. arterial blood.[8]

The arterial oxygen content (Column 3) represents the cubic centimeters of oxygen combined with hemoglobin in 100 cc. of the arterial blood; the percentage saturation of arterial blood (Column 4) indicates the degree of oxygenation of the hemoglobin.

The difference between oxygen content and total oxygen capacity has been called by Lundsgaard[9] the "oxygen unsaturation," and the values for this are given in the fifth and seventh columns, headed respectively "arterial oxygen unsaturation" and "venous oxygen unsaturation."

The sixth column, "oxygen content of venous blood, represents the cubic centimeters of oxygen combined with hemoglobin in 100 cc. of the venous blood.

Lundsgaard and Van Slyke[10] show that it is the capillary blood which produces the cyanotic color in the skin. Since neither the arterial nor the venous ends of the capillaries are truly representative of capillary blood, Lundsgaard has used the mean between arterial and venous unsaturation to represent the mean capillary unsaturation, and we have followed his use of the term (Column 8).

The difference between the oxygen content of 100 cc. arterial blood and 100 cc. venous blood has been termed oxygen consumption by many writers and is applied similarly here (Column 9).

The carbon-dioxide content of arterial blood (Column 10) represents the cubic centimeters of carbon dioxide in 100 cc. arterial blood and a similar value is given for venous blood (Column 11).

Hemoglobin was determined by the Newcomer method, and the results are given as grams hemoglobin per 100 cc. whole blood (Column 16).

Clinical Findings. An inspection of Table IV will show that the oxygen capacity (Column 2) of these subjects varies within normal limits. The arterial oxygen content (Column 3), however, is in almost every case less than would be expected from the total oxygen capacity of the blood. This results in an arterial oxygen unsaturation (Column 5) which is greater than normal. Stadie[5] finds a mean arterial unsaturation of 1 volume per cent in a group of 5 normal individuals, and in no case is there an arterial oxygen unsaturation of over 1.4 volumes per cent. Harrop,[11] in a series of 15 normal individuals, shows a variation in arterial oxygen unsaturation of 0 to 1.08 volumes per cent. The 2 normal individuals of the group at present under consideration, Cases 15 and

16, showed values of 0.47 and 1.26 volumes per cent arterial oxygen unsaturation respectively, thus coinciding with the other normal findings in the literature. The arterial unsaturation of the psychotic group, however, showed abnormally high values in 9 out of 14 cases. Six of the patients, Cases 2, 8, 11, 12, 13 and 14, revealed an arterial unsaturation exceeding 2 volumes per cent. As a consequence of this arterial oxygen unsaturation, the percentage unsaturation of arterial blood (Column 4) is low. The range of percentage saturation in Harrop's series is 94.4 to 100 per cent. The figures for the normal individuals of the present series are 97.6 and 94.2 per cent. Of the 14 patients in the psychotic group 12 showed arterial blood that was less than 95 per cent saturated with oxygen and 6 of these were below 90 per cent. These findings, together with those of the succeeding columns, will be considered more fully in the discussion.

The oxygen content of the venous blood (Column 6) appears rather low also. This value represents, according to Lundsgaard,[12] Greene and Greene[13] and others, the reserve oxygen of the organism. As long as the hemoglobin exceeds the minimum (about 30 per cent, corresponding to an oxygen combining power of 5.5 volumes per cent) there will be a supply of reserve oxygen, its quantitative value depending on the oxygen content of arterial blood. The normal value for this reserve in the resting individual is 13 volumes per cent. In our cases the oxygen content of venous blood ranged from 4.48 to 14.2 volumes per cent.

The venous oxygen unsaturation (Column 7), which represents the difference between the total oxygen capacity of the blood and the oxygen content of the venous blood, is therefore high. With the normal saturation of the arterial blood, 95 to 100 per cent, the normal venous unsaturation closely approximates the oxygen consumption by the tissues, but in these cases the preponderance of abnormal arterial unsaturation caused a varying discrepancy between the two.

Lundsgaard has stated that "cyanosis is not associated with values of the oxygen unsaturation below about 8 volumes per cent (7.93 volumes per cent in one case). This is of no considerable importance because the upper limit of oxygen unsaturation in resting normal individuals has previously been found to be about 8 volumes per cent." In our series the venous oxygen unsaturation was in most cases greater than 8 volumes per cent. Indeed, 11 of the subjects showed an unsaturation greater than 10 volumes per cent. In 3 of the cases, however, the unsaturation was less than 8 volumes per cent.

The mean capillary unsaturation (Column 8), which represents the closest approximation to the average unsaturation of the capillary blood that we can obtain, is also generally high. Lundsgaard[15] gives the average as between 2 and 3 volumes per cent,

although cyanosis does not ordinarily appear until it has reached 6 to 7 per cent. In our series it was greater than 6 volumes per cent in almost all cases, but there were a few individuals whose mean capillary unsaturation was less than 6 volumes per cent.

The oxygen consumption (Column 9) represents the difference between the oxygen content of the arterial blood and the oxygen content of the venous blood. It, therefore, under normal conditions, closely approximates the venous oxygen unsaturation (Lundsgaard[15]). In our cases, due to the frequent initial arterial oxygen unsaturation, the oxygen consumption is commonly much less than the venous oxygen unsaturation. Despite this discrepancy, the values for oxygen consumption are for the most part, greater than those obtained by Stadie, Harrop and others.

Both the carbon dioxide content of the arterial blood (Column 10) and the carbon-dioxide content of the venous blood (Column 11) agree with the normal findings in the literature. Krehl[16] has mentioned an abnormal retention of carbon dioxide in cyanotic individuals, but our findings are within normal limits.

The temperature, pulse and respiration records taken just previous to the puncture are given in Columns 12, 13 and 14. A more intensive and prolonged series of readings are given under clinical findings.

The red blood cell count (Column 15) shows a slight but constant difference between the arterial and venous bloods. Unfortunately, the blood samples were not always sufficient to permit of blood counts, but in all cases in which both arterials and venous counts were made the venous blood showed a greater number of corpuscles. True, the increase is slight, but it is interestingly constant. The sequence was frequently reversed, the venous counts being made before the arterial on one day, and the arterial samples counted first the next day, but the venous counts were invariably greater. The capillary counts were normal. Since they were performed outside the laboratory by another worker, they cannot be expected to check perfectly the venous and arterial counts. The capillary blood was not oxalated, whereas the tubes in which the venous and arterial blood were kept had been coated with a 0.2 per cent solution of potassium oxalate aërated to dryness. It has been found, however, by Foord[17] and others that oxalate in such low concentration exerts no appreciable influence upon the blood count of freshly drawn blood.

The hemoglobin measures in grams per 100 cc. blood (Column 16) corresponds to the normal values in the literature.

Discussion. It will be seen from the foregoing results that, although the oxygen capacity of the blood was normal, even in some cases a little high, the actual content of the arterial blood was low in almost all cases. Low arterial oxygen contents have been found in patients suffering from pneumonic infiltration of the

lungs, intraventricular heart lesions and other organic disturbances. The physical examinations of the patients in the present series, however, show no heart or lung conditions to account for the low-oxygen tension. It will be seen from Table II that there was a lack of increase in the heart rate after exercise as compared with the rate of normal subjects (Table II*b*). It is also known that the incidence of tuberculosis is very high among cases of dementia praecox. Whether there is any relationship between these facts and the low arterial oxygen content remains to be ascertained. Lundsgaard has found low arterial oxygen contents in patients suffering from polycythemia. A few of our patients showed arterial oxygen capacities which approached the high normal limit, but the blood counts were normal in all cases. Low arterial oxygen tension was generally accompanied by an extreme degree of cyanosis, but there are three examples of low oxygen tension accompanied by a moderate degree of cyanosis. These are: Case 11, with an arterial saturation of 88.4 per cent; Case 12, with an arterial saturation of 84 per cent; Case 13, with an arterial saturation of 84.2 per cent. Lundsgaard has shown that the cyanotic color is in a measure dependent on individual peculiarities of the skin, membranes, etc., and the fact is, therefore, not as striking as it first appears.

The high arterial oxygen unsaturation is, of course, a corollary to the low arterial oxygen content. The low venous oxygen content was also to be expected with its attendant high venous oxygen unsaturation.

The mean capillary unsaturation was, considering the degree of cyanosis, not conspicuously high in most instances. However, Lundsgaard has stated that: "(1) An abnormally high oxygen unsaturation of the blood results in the clinical condition known as cyanosis. (2) That this increased oxygen unsaturation may be produced in two ways: (*a*) By an increased reduction of oxyhemoglobin to reduced hemoglobin in the peripheral capillaries; (*b*) by an incomplete oxidation of the venous blood in the lungs." He has also shown that cyanosis occurs at a lower mean capillary unsaturation when caused by incomplete oxidation in the lungs than when resulting from increased reduction of oxyhemoglobin in the peripheral capillaries. Since the oxidation of the venous blood in the lungs of our patients was manifestly incomplete, the low mean capillary unsaturations are in accordance with Lundsgaard's findings.

The figures for oxygen consumption are for the most part greater than the normal value. This indicates that a condition obtained in the capillaries during which an increased reduction of the oxyhemoglobin took place in accordance with (*a*) above. Palpation gave the impression that the arteries were of smaller diameter than the average. This fact has been observed before in psychiatric literature. Also the walls were very soft and easily compressed.

The increased reduction of oxyhemoglobin may have been caused by stasis in the vessels due either to relaxed walls or to congestion on account of the small diameter.

Both of the factors mentioned by Lundsgaard above were then operating to produce the cyanosis of these patients.

The carbon dioxide content of both arterial and venous blood was normal. According to Lundsgaard,[9] however, there is no relationship between the carbon dioxide content and cyanosis.

The temperature, pulse and respiration records have been discussed under Clinical Findings.

The red blood cell count is normal and consistent with both oxygen capacity and hemoglobin. The values for hemoglobin are in the large consistent with the oxygen capacity. They cannot be translated mathematically in terms of each other. The method generally has been to multiply the grams hemoglobin by 1.34 to obtain volumes per cent oxygen capacity. However, the value 1.34 was not obtained in the blood of man, and it is, therefore, not surprising that such multiplication does not exactly coincide with the value for oxygen capacity obtained by direct analysis of the blood of man.

Summary. Examination of the gas relationships in the blood of young male dementia praecox patients with cyanosis revealed the following:

1. The oxygen capacity was normal.
2. The oxygen content was below normal and the blood showed a consequent arterial unsaturation.
3. The oxygen consumption was high.
4. The cyanosis, therefore, appears to be the result of: (*a*) Incomplete oxidation of blood in the lungs; (*b*) increased reduction of oxyhemoglobin to reduced hemoglobin in the peripheral capillaries.
5. The mean capillary unsaturation approached the low limit for cyanosis. This condition has also been found in pneumonia and influenza where there is an incomplete oxidation of blood in the lungs.
6. The red blood cell count showed a slight, but uniform increase in the corpuscles of venous over arterial blood.
7. The patients after being subjected to exercise showed surprisingly little increase in the heart rate.

In conclusion, we wish to acknowledge our indebtedness to Dr. D. D. Van Slyke, Dr. B. Hastings, Dr. C. Lundsgaard and Dr. C. Binger, of the Rockefeller Institute, for frequent advice and helpful suggestions; also to Dr. Ernst Boas, of Montefiore Hospital, and Dr. Charles W. Fairchild, of New York, for reading the Roentgen ray plates.

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ISOLATED BILATERAL PARALYSIS OF THE GLOSSOPHARYNGEAL NERVE DUE TO CEREBRAL SYPHILIS.

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Isolated paralysis of the glossopharyngeal nerve in syphilis, or indeed in any other condition, is an extremely rare finding. Involvement of this nerve is found rather frequently in processes which involve contiguous nerves such as the tenth, eleventh and twelfth cranial nerves, but a pathologic process of any sort which causes disease of the glossopharyngeal nerve alone has been reported in strikingly few instances. Indeed, Oppenheim[1] believes that "isolated disease of this nerve has practically never been observed." Nonne[2] remarks that "reports of isolated disease of this nerve have never come under my observation, but in all the pathologic processes which involve the last four cranial nerves, whether in the nuclear region or in the root sphere inside or outside of the medulla, it may also be affected." Others too agree that isolated involvement of

the glossopharyngeal is rare. Stewart[3] states that "isolated paralysis of the glossopharyngeal nerve is practically unknown." Jelliffe and White[4] believe that peripheral lesions of the glossopharyngeal nerve are rare save from war wounds, and Church and Peterson[5] remark that "practically, in man, it is never alone diseased." Doyle,[6] who investigated the question of glossopharyngeal neuralgia, believes that "lesions of the glossopharyngeal nerve, experimental or acquired, are extremely rare." Finally, Spiller[7] says that "isolated paralysis of this nerve seems never to occur."

There have been reported a few cases in which intracranial disease involved only the glossopharyngeal nerve. Neve,[8] following the work of Ramsay Hunt on the geniculate ganglion, reported a case which he termed herpes zoster of the glossopharyngeal nerve. Inasmuch as there was simultaneous involvement of the ipsolateral seventh and eighth nerves in this case, one can hardly consider it an example of isolated involvement of the glossopharyngeal. Oppenheim[9] reports a case which he himself did not consider a pure ninth nerve paralysis, but which showed a predominance of ninth nerve symptoms. His patient complained of loss of taste in the throat and posterior part of the tongue, together with a loss of temperature appreciation in these loci. Objectively, there was a slight paresis of the palate and throat muscles with decreased reflex action, a loss of taste over the soft palate, throat, and posterior tongue region, as well as loss of temperature in this region. Touch was intact. The case occurred after influenza, and Oppenheim attributes it to a chemical effect on the endings of the glossopharyngeal nerve. In 1923, Doyle[6] described 4 cases of glossopharyngeal neuralgia, a condition which had previously been described by Sicard and Robineau and by Harris. In this atypical form of neuralgia, section of the glossopharyngeal nerve and the pharyngeal branches of the tenth led to a complete disappearance of the pain, indicating an isolated ninth nerve involvement for the most part.

It is because of the extreme rarity of involvement of this nerve that the following case is reported as an isolated bilateral paralysis of the glossopharyngeal nerve occurring in cerebral syphilis and disappearing completely with specific treatment.

Report of Case. *History.* E. J., a white male, aged sixty-three years, entered the Philadelphia Orthopedic Hospital and Infirmary for Nervous Diseases on the service of Dr. C. W. Burr, in April 1924, complaining of trouble with swallowing for eleven days. The family history showed that the father had died at the age of seventy-two years, and the mother at fifty-nine years, of unknown causes. One sister had died at the age of sixty-three years, of diabetes, one brother at fifty years, of chronic alcoholism, and one brother at forty-seven years of inflammatory rheumatism.

The patient stated that he had been in excellent health all his life, and save for some stomach trouble in 1917, which cleared up after ten days, he had never been ill before. At the time of onset

of his illness he was working as a stationary engineer. He had worked at this for twenty years, but previous to this he had roamed about the oil fields of Indiana, Ohio and Oklahoma for fourteen years. The patient denied either syphilitic or gonorrheal infection. He said that he was perfectly well until eleven days before entrance into the hospital in April, 1924, when he found that he could not swallow solid food. He managed to eat some dinner consisting of chicken, biscuit and strawberries, but he ate much less than his usual course. By evening his swallowing was much worse. He could eat a little solid food by "worrying it down," but with great difficulty. He had no difficulty in swallowing liquids, but he felt that he had to keep swallowing once he started, and he found it hard to keep the last gulp down. At the time of entrance he felt he was getting worse. He denied any memory or personality changes, and insisted that except for his swallowing he was perfectly well.

General Examination. A very-well preserved white man, aged sixty-three years, with a smooth, paretic facies. The head, ears and nose were negative. The lower incisors were carious; the upper teeth were false. The heart showed a slight enlargement of the supracardiac area, and an accentuated aortic second sound. The blood pressure was 164 systolic and 90 diastolic. The peripheral vessels were definitely sclerosed. The lungs and abdomen were negative. The extremities showed clubbing of the fingers and toes.

Neurologic Examination. The cranial nerves showed the following: The right pupil was irregular, both pupils were small and equal; both were almost stiff to light, but reacted in accommodation. Examination of the fundi was negative. The glossopharyngeal nerve on both sides was paralyzed. This was shown subjectively by an inability to swallow. Objectively, there was complete anesthesia of the upper part of the pharynx, posterior part of the tongue and of the tonsils and difficulty in swallowing which was almost complete. The palate on either side showed no movement. Solids could not be swallowed, while liquids were gulped down. There was no disturbance in taste. The patient could identify all objects placed on the back of his tongue, and complained of no subjective gustatory difficulties. The first, third, fourth, sixth, seventh, eighth, tenth, eleventh, and twelfth cranial nerves were entirely normal. The reflexes showed hyperactive knee jerks, and absent abdominal reflexes, but were otherwise normal. There was no ankle or patellar clonus, no Oppenheim or Babinski. The motor system was entirely negative. The gait was normal. The speech was somewhat hesitating, but this was attributed to poorly fitting false teeth.

Laboratory Findings. Blood: Erythrocytes, 4,880,000; hemoglobin, 78 per cent; leukocytes, 10,000. Blood chemistry: Urea, 25 mg. per 100 cc.; nonprotein nitrogen, 18 mg. per 100 cc.; sugar, 136 mg. per 100 cc. Basal metabolism was 1.5. The urine on several occasions was entirely negative for sugar and other abnormalities. The blood Wassermann test was 4+ in the cholesterin

fortified antigen, and negative with the alcohol and lipoid antigens. The spinal fluid on the first examination May 7, 1924, showed 57 cells, a 3+ globulin, a colloidal-gold test of 4555421100, and a 4+ Wassermann test with dilutions of 0.3, 0.5, 0.8, and 1 cc. One week later it contained 61 cells, a 4+ globulin, a colloidal-gold test of 455541110, and a 4+ Wassermann test in all antigens.

Treatment and Course. The patient for several days had great difficulty in swallowing anything except liquids. He showed a slight improvement after one week, however. At this time he was given potassium iodide in increasing doses beginning with 10 gr. three times a day. This was increased so that at the time of his discharge he was receiving 30 gr. three times a day. He also received two injections of neoarsphenamin in doses of 0.6 mg., under which treatment he gradually improved. His swallowing reflex returned, and the anesthesia of the palate and pharynx gradually disappeared until three weeks after the inception of treatment he was perfectly well as far as the swallowing was concerned. The patient was discharged from the hospital but he returned every week for treatments of neoarsphenamin. He continued taking his iodid of potassium. When seen about eighteen months after his discharge he was perfectly well. No further serologic studies were made.

Discussion. Two points of interest are presented by our case, namely: The isolated involvement of the glossopharyngeal on a syphilitic basis and the preservation of taste over the posterior third of the tongue. Syphilis is conceded by most authors as a cause of involvement of the ninth cranial nerve. Stewart,[3] Oppenheim[1] and Tilney[9] all mention it as an important factor in disease of this nerve. And yet with a perfectly specific cause it is difficult to see how the glossopharyngeal nerve alone could be selected in the disease process. It is unlikely that the lesion was a basilar meningitis because in this event the tenth and eleventh cranial nerves would undoubtedly have been involved also. It is far more likely that the lesion was situated in the motor portion of the glossopharyngeal nucleus, that is, in the nucleus ambiguus. It is probable also that the cells of the ninth, tenth, and eleventh nerves have a distinct representation in the nucleus ambiguus, just as do the cells supplying the muscles of the eyeball in the oculomotor nucleus. Spiller,[7] in a discussion of a case of paralysis of the ninth, tenth and eleventh nerves says: "It would seem reasonable to assume that structures so remote from one another as the soft palate and vocal cords have different representation in the central nervous system, although a distinct group of cells for each structure might be included within the nucleus of the same cranial nerve." If one concedes this, it does not seem unreasonable to assume isolated involvement of the ninth nerve cells in the nucleus ambiguus especially on a syphilitic basis.

To explain the preservation of taste over the posterior third of

the tongue in this case is a very difficult matter. One might assume however that the nucleus tractus solitarius which is the center for taste of the glossopharyngeal nerve, was not affected. The question of the distribution of taste fibers is still a disputed point, and one which we do not feel competent to discuss, but evidence can be adduced to show that taste is not uniformly affected in disease of the glossopharyngeal nerve. For example, Wessely[10] reported a case of involvement of the ninth and tenth nerves on one side with preservation of taste sensation, and Oppenheim[1] remarks conclusively that "no case has been observed which proves with certainty that the posterior taste fibers are contained in the glossopharyngeal nucleus or in the roots of this nerve." Cassirer[1] has reported a case which show that all the taste fibers may run in the glossopharyngeal, while on the other hand, Mönch[1] described a case of gunshot injury of the left side of the head with loss of taste on the left side of the tongue in which the glossopharyngeal was intact. Doyle, on the other hand, reported absence of taste following evulsion of the glossopharyngeal branch of the tenth. He accepts Luciani's statement that taste fibers are derived entirely from the ninth nerve. In our case, however, there was unquestionable involvement of the glossopharyngeal nerve with preservation of the sense of taste, due probably to escape of the nucleus tractus solitarius in the disease process, and to involvement either of the dorsal nucleus or the nucleus ambiguus.

Summary. A case is presented of a white male, aged sixty-three years, who complained of trouble in swallowing solid food, who showed definite bilateral paralysis of the glossopharyngeal nerve with involvement of no other cranial nerves and with preservation of taste over the posterior third of the tongue. There was evidence of syphilis clinically and serologically, and under specific treatment the paralysis disappeared and has not recurred. In all probability there was no involvement of the tractus solitarius, and there were probably definite lesions either in the dorsal nucleus or in the nucleus ambiguus.

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REVIEWS.

MODERN MEDICINE: ITS THEORY AND PRACTICE. Edited by SIR WILLIAM OSLER, BART., M.D., F.R.S. Third edition thoroughly revised; reëdited by THOMAS MCCRAE, M.D., Professor of Medicine in the Jefferson Medical College, Philadelphia. Volume II. Pp. 891; 105 illustrations and 5 plates. Philadelphia: Lea & Febiger, 1925. Price, $9.00.

THIS volume begins with the diseases of unknown etiology, a group from which three have been removed since the last edition—scarlet fever, yellow fever and rat-bite fever. Then comes a section on the protozoan infections, with a new chapter on the leishmaniases. The section on spirochetal infections now offers a formidable list: Syphilis, frambesia, the relapsing fevers, yellow fever, spirochetosis icterohemorrhagica and rat-bite disease. There are sections on the diseases caused by animal parasites, diseases due to physical agents and those due to chemical and organic agents. In the latter group, under the heading of "Food Poisoning and Food Infections," have been included bacterial food infections and bacterial food intoxication (botulism). This chapter has appended to it a list of thirty-three important references, a feature that would be most desirable in all parts of the work. The volume closes with a new section on Deficiency Diseases, including pellagra, beriberi, scurvy and rickets. The revisions are thorough and accurate, and there is the same tendency slightly to shorten articles that was shown in the first volume. R. K.

THE BIOLOGY OF THE PROTOZOA. By G. N. CALKINS, Professor of Protozoölogy, Columbia University. Pp. 623; 238 engravings. Philadelphia: Lea & Febiger, 1926. Price, $7.50.

THE title of this new book on protozoa indicates the author's point of view. In the first five chapters a general account is given of structure, physiology and reproduction. Chapters VI to IX deals with taxonomy and include extensive keys for the identification of common genera, both parasitic and free-living. The headings of Chapters X to XII are, respectively, "Vitality," "Phenomena

Accompanying Fertilization" and "Effects of Reorganization on Vitality." In these last three chapters the theory of the "life cycle" (youth, maturity and old age) is supported by extensive examples, citations and discussions which should interest both medical and zoölogical scientists. The book is beautifully manufactured and extensively illustrated. D. W.

THE DISEASES OF CHILDREN. By the late SIR JAMES FREDERICK GOODHART, BART., M.D., LL.D. (ABERD.), F.R.C.P. Twelfth edition edited by GEORGE FREDERICK STILL, M.A., M.D., F.R.C.P., Professor of Diseases of Children, King's College, London; Physician for Diseases of Children, King's College Hospital; Physician to the Hospital for Sick Children, Great Ormond Street. Pp. 966; 68 illustrations. Philadelphia: Lea & Febiger, 1926. Price, $8.50.

FIRST written in 1885 by the late Sir James Goodhart, this book has reached its twelfth edition, an adequate evidence of its worth and popularity. The new edition has been edited and revised by Professor Still, who has accomplished his task for the most part very satisfactorily. The reviewer, however, misses reference to the work of Dick and of Dochez on scarlet fever, to platelet alterations in hemophilia and purpura and the allergic factor in infantile eczema. The type is clear and pleasing, as is also the makeup of the book, and it will continue to be popular with student and practitioner.

R. K.

MEDICAL HEREDITY: DISTINGUISHED CHILDREN OF PHYSICIANS (UNITED STATES, TO 1910). By WILLIAM BROWNING, PH.B., M.D., Professor of Neurology, Long Island Medical College; Consultant to the Brooklyn State and other hospitals. Pp. 250. Baltimore: The Norman, Remington Company, 1925. Price, $4.00.

THE author of this peculiar book has elected to pick out 3000 "distinguished" children of physicians and classify them, with two or three descriptive lines apiece, into some forty odd branches of human endeavor, to serve as a basis for a number of rather far-reaching conclusions. Aside from the obvious, insuperable obstacles in the way of collecting complete data on such a topic, one may well inquire at the outset, what forms his criterion of distinction? Of many entries there can be no question; but of still more the standard must have been so lenient that the method at once loses most of its value when applied, for instance, to such questions as regional influence, choice of profession, eugenics and so forth. Furthermore, as the author himself recognizes, a control comparison

with children of men of other callings is out of the question, so that deductions are limited to the data collected. Maternal influence is practically entirely disregarded. Such limitations would seem to rob the book of its scientific value as a study in heredity. What one might call some of its by-products, however, are not without interest. The index of six thousand names renders a large amount of up-to-date biographic material available. If not taken too seriously, the discussion of the handicaps and advantages of physicians' children, what profession they are suited for, the effect of alcohol, and so forth, afford pleasant reading; finally, as the author rather obscurely adds, the book "may serve in repelling thrusts by those addicted to twicking the doctors." E. K.

REJUVENATION BY GRAFTING. By SERGE VORONOFF, M.D., Director of the Department of Experimental Surgery of the College of France; Assistant Director of the Biological Laboratory at the Ecole des Hautes Etudes. Pp. 221; 38 illustrations. New York: Adelphi Company, 1925.

IT is difficult to write an appreciation and easy to pen a criticism of this book. Written undoubtedly so the lay reader may assimilate, it abounds in physiologic incongruities and unproven dicta, lacks scientific presentation, makes illogical statements and numerous errors. On the other hand, it is a pleasure to correct a misunderstanding in regard to our interpretation of the author's work and to state that he constantly contends that his method produces its greatest benefits in other physiologic spheres than the sexual, and that it is not an aphrodisiac.

He presents first the development of the idea, then argues the case of homografts *versus* heterografts to the conclusion that his belong to neither, and so invents the "homeograft." Third, he describes his operation and then cites the histories of his 44 cases. He admits 2 failures. Though his experimental animals showed the height of rejuvenated function at eighteen months, and his "true cases of testicular insufficiency" "were unaware of any sense of benefit for two, three or even five months," and states that "I never give an opinion on the results of a graft before the third or fourth month," an analysis of his case histories shows final favorable (?) reports in 28 per cent before the expiration of the second postoperative month and in 43.6 per cent before the end of the third month. The last third of the book is an appendix containing eleven communications by the author and his associates to various societies.

It is not one's desire to be excessively critical, nor to deny that concerning which one is unfamiliar, but this book will not appeal to the scientific medical reader. A. R.

APPLIED BIOCHEMISTRY. By WITHROW MORSE, PH.D., Jefferson Medical College, Philadelphia. Pp. 958; octavo, with 257 illustrations. Philadelphia and London: W. B. Saunders Company, 1925. Price, $7.00.

BY concentrating on the more purely medical phases of biochemistry, the author has succeded in eliminating many of the objectionable features characteristic of the textbooks now in use, and, consequently, *Applied Biochemistry* is a book well adapted to the uses of the student of medicine. While the medical applications of biochemistry are the dominant feature, fundamentals are not neglected, the entire book being written in a spirit of commendable thoroughness, which includes much recent work of importance. A large number of original references to the literature are included in the footnotes, serving to stimulate further inquiry on the part of the reader. An interesting feature is the inclusion of numerous biographic notes and pictures of leading biochemists, together with brief summaries of their chief contributions. Also deserving mention are the diagramatic summaries at the ends of chapters. Clinical and laboratory methods received considerable attention, and are, with a few exceptions, the best available.

J. R.

RESPIRATORY FUNCTION IN DISEASE. By JONATHAN C. MEAKINS, M.D., C.M. (MCGILL), F.R.C.P. (EDIN.), F.R.S. (EDIN.), Professor of Medicine, McGill University, and Physician-in-Chief to the Royal Victoria Hospital, Montreal; formerly Christison Professor of Therapeutics in the University of Edinburgh; and H. WHITRIDGE DAVIES, M.B., B.S. (ADELAIDE), Lecturer in Methods of Clinical Investigation in the Department of Therapeutics, University of Edinburgh. Pp. 478; 63 graphs. Edinburgh and London: Oliver & Boyd, 1925.

THE respiratory function includes all the steps in the carrying of carbon dioxid and oxygen between the outer air and the tissues and involves pulmonary ventilation, the circulation and the tissue metabolism. Our knowledge of the physiology of this important function in health and disease has progressed so rapidly in two decades that this is a most timely summary for the practioner and teacher of medicine. The author has admirably brought together the important studies especially from Great Britain, Denmark and the United States, and has exhibited nice critical judgment in assigning to each its due significance. The author avoids the use of mathematical notation which is often difficult for workers not familiar with this special field.

J. A.

METHODS AND PROBLEMS OF MEDICAL EDUCATION. First, second and third series. Pp. 150, 118 and 242. Published by the Division of Medical Education of the Rockefeller Foundation, 61 Broadway, New York, 1924.

RECOGNIZING the increasing difficulties in the way of disseminating information about medical education, the Rockefeller Foundation has begun "to collect and publish from time to time brief descriptions of clinics, laboratories and methods of teaching in different parts of the world." The first of the series contains twelve articles on new institutes and methods of teaching in seven different countries of the world. In the second series are two articles on sanitary surveys by Rosenau and by Shields Warren, and in the third nineteen articles on institutes and departments, chiefly of anatomy, physiology and pathology. The volumes or separate reprints are to be had for the asking from the Rockefeller Foundation and are worth more than that to anyone interested in medical education or about to plan a new department. E. K.

ON WRITING THESES FOR M.B. AND M.D. DEGREES. By SIR HUMPHRY ROLLESTON, BART., K.C.B., HON. D.SC. (OXFORD), D.C.L. (DURHAM), LL.D. (GLASGOW and BRISTOL), Regius Professor of Physics in the University of Cambridge and President of the Royal College of Physicians of London. Pp. 28. London: John Bale, Sons & Danielsson, Ltd., 1925.

ALTHOUGH the advice given in this pamphlet is primarily for British medical students, it is of equal value to Americans. As with the authors recommended as models, there is not a superfluous word. It is perhaps more than a coincidence that the models of style to whom reference is made are all British, whereas the recommended compilations and books of instruction are with one exception all American. E. K.

CORRECTION.

In the review of Bailey's Textbook of Histology in the March number of this JOURNAL, page 440, the statement was incorrectly made that "the important recent development of the reticulo-endothelial system seems to have escaped the revisers' attention." There is actually a very good six-page review on page 80 of the book as well as a few casual references elsewhere.

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EARS AND THE MAN. By Annette W. Peck, Estelle E. Samuelson and Ann Lehman. Pp. 217. Philadelphia: F. A. Davis Company, 1926. Price, $2.00.

ACUTE INFECTIOUS DISEASES. By J. D. Rolleston, M.A., M.D. (Oxon.). Pp. 376. Physicians and Surgeons Book Company, 1926.

OPERATIVE CYSTOSCOPY. By E. Canny Ryall, F.R.C.S. Pp. 46; 670 illustrations. St. Louis: C. V. Mosby Company, 1926. Price, $25.00.

THE ART AND PRACTICE OF MEDICAL WRITING. By George H. Simmons, M.D. and Moris Fishbein, M.D. Pp. 163; 21 illustrations. Chicago: American Medical Association, 1925.

SURGICAL CLINICS OF NORTH AMERICA. Philadelphia Number, December, 1925. Pp. 223; 50 illustrations. Philadelphia: W. B. Saunders Company, 1925.

PRESCRIPTION NOTES. By Arthur L. Tatum, Ph.D., M.D. Pp. 22. Chicago: University of Chicago Press, 1926.

PUBLIC HEALTH LAW. By James A. Tobey, M.S., LL.B. Pp. 304. Baltimore: Williams & Wilkins Co., 1926. Price, $4.50.

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PYGMALION OR THE DOCTOR OF THE FUTURE. By R. M. Wilson, M.B., Ch.B. Pp. 67. E. P. Dutton & Co., 1926. Price, $1.00.

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LA ARTERITIS PULMONAR CARDIACOS NEGROS. By F. C. ARRILLAGA Pp. 274; 50 illustrations. Buenos Aires, Libreria (El Ateneo), 1925.

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FACTS ON THE HEART. By R. C. CABOT, M.D. Pp. 781; 163 illustrations. Philadelphia: W. B. Saunders Company, 1926. Price, $7.50.

KIDNEY DISEASE. By ROLFE FLOYD, M.D. Pp. 181. New York City: James T. Dougherty, 1926.

GOULD AND PYLE'S POCKET CYCLOPEDIA OF MEDICINE AND SURGERY. Third edition. Pp. 922. Philadelphia: P. Blakiston's Son & Co., 1926. Price, $2.50.

MEDICAL DIAGNOSIS FOR THE STUDENT AND PRACTITIONER. By CHARLES LYMAN GREENE, M.D. Pp. 1468; 14 colored plates and 709 other illustrations. Philadelphia: P. Blakiston's Son & Co., 1926.

GUY'S HOSPITAL REPORTS, 1926. VOL. LXXVI. A. F. HURST, M.D., Editor. Pp. 126; illustrated. London: Wakley & Son, Ltd., 1926. Price, $3.50.

COMPARATIVE PHYSIOLOGY. By LANCELOT T. HOGBEN, M.A. (CANTAB.), D.SC. (LOND.). (A short presentation of Response, Metabolism, Coördination and Reproduction intended to supplement Winterstein's *Vergleichende Physiologie* and stimulate the young to "dip into" this field.) Pp. 219; 44 illustrations. New York: The Macmillan Company, 1926.

SIXTY YEARS IN MEDICAL HARNESS. By CHARLES B. JOHNSON, M.D. Pp. 345; 16 illustrations. New York: Medical Life Press, 1926. Price, $3.00.

THE PATHOLOGY OF TUMORS. By E. H. KETTLE, M.D., B.S. (LOND.). Pp. 285; 159 illustrations. New York: Paul B. Hoeber, Inc., 1926. Price, $5.00.

BACTERIOLOGY AND APPLIED IMMUNITY FOR NURSES. By ROBERT A. KILDUFFE, A.B., M.A., M.D. Pp. 252; 79 illustrations. Milwaukee, Wis.: The Bruce Publishing Company, 1926. Price, $2.00.

VISUAL FIELD STUDIES. By RALPH I. LLOYD, M.D., F.A.C.S. Pp. 216; 124 illustrations. New York: The Technical Press, 1926. Price, $6.00.

PHYSIOLOGICAL AND CLINICAL CHEMISTRY. By WILLIAM A. PEARSON, PH.C., PH.D., M.D., and JOSEPH S. HEPBURN, A.M., B.S. (CHEM.), M.S., PH.D. Pp. 306; illustrated. Philadelphia: Lea & Febiger, 1926. Price, $4.00.

SELECTED CONTRIBUTIONS FROM THE PEKING UNION MEDICAL COLLEGE. VOL. V. Peking, China.

OPHTHALMIC NEUROMYOLOGY. By G. C. SAVAGE, M.D., LL.D. Second edition. Pp. 227; 51 illustrations. Nashville, Tenn.: The Author, 1926. Price, $3.00.

SILICOSIS. Special Bulletin, Department of Labor, State of New York, 1925. Bureau of Industrial Hygiene, Leland E. Cofer, M.D., Director. Pp. 68; 1 illustration. Gratis.

CHEMISTRY AND RECENT PROGRESS IN MEDICINE. By JULIUS STIEGLITZ. Pp. 62. Baltimore: Williams & Wilkins Co., 1926.

THE MEDICAL DEPARTMENT OF THE UNITED STATES ARMY IN THE WORLD WAR. VOL. VIII: FIELD OPERATIONS. Prepared under the direction of MAJOR-GENERAL M. W. IRELAND, the Surgeon-General. By COL. CHARLES LYNCH, M.C., COL. JOSEPH H. FORD, M.C., and LIEUT.-COL. FRANK W. WEED, M.C. Pp. 1097; 99 illustrations. Washington, D. C.: Government Printing Office, 1925.

METHODIK DER UNTERSUCHUNGEN VON NERVENELEMENTEN DES MAKRO- UND MIKROASKOPISCHERT GEBIETES. Part I. By PROF. DR. W. WOROBIEW. Pp. 130; 39 illustrations. Berlin: Oscar Rothacker, 1926.

YOUNG'S PRACTICE OF UROLOGY. By HUGH H. YOUNG, M.D., and DAVID M. DAVIS, M.D. Pp. 1484; 1003 illustrations. Philadelphia: W. B. Saunders Company, 1926. Price, $25.00 for the two volumes.

PROGRESS

OF

MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF

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Cancer Mortality.—Two reports have recently been received which present some interesting statistics carefully compiled on the mortality of cancer. The first of these is a biometric study by the statistician of the Metropolitan Life Insurance Company, L. I. DUBLIN (*Cancer Mortality among Insured Wage Earners and their Families,* 1025). The outstanding facts disclosed by the analysis of the death rate among the insured are detailed in a large number of tables and are summarized as well in round figures in the report. These figures show that from 1911 to 1922 cancer was the fifth cause of death in numerical importance, heart disease, tuberculosis, nephritis and pneumonia alone outranking cancer, while in 1921 only heart disease and tuberculosis exceeded this disease. The expectancy of cancer in a male child, aged ten years, is 8 in 100; in a female, 11 in 100. There is a significant upward trend in those of both sex who have passed fifty-five years. More than 2 per cent of all cancer (sarcoma also?) deaths in policyholders were of persons under twenty-five years. Deaths from cancer of the liver, the intestinal tract and the female genitals constitute over two-thirds of the mortality from cancer. Cancer of the liver and stomach is the cause of death in about the same number of males as females, but cancer of the peritoneum, intestines and rectum is much higher among women than men and, together with the large number of deaths from cancer of the genital organs and breast, accounts for the greater incidence of death from cancer in women than in men. Of interest is the upward trend of the death rate from can-

cers of the intestinal tract, which is more pronounced than for any other group of malignant growths. More than 60 per cent of deaths in this group were the result of growths in the small or larger intestine other than the rectum or anus, which in turn accounted for 31 per cent of deaths. Breast cancers cause 13.5 per cent of all deaths from cancer among white females. Cancer of the buccal cavity caused the death of 8.9 per cent of white males. The second report by J. W. SCHERESCHEWSKY (*U. S. Pub. Health Rept.*, 1926, **41**, 1) recounts the cancer mortality in the ten original registration states. The ten original registration states were selected because these were the only states in which continuous records have been kept for a period of twenty-one or more years. Furthermore, the population in these states is a homogeneous one, at least as free from diverse racial stocks as any other group in the country. As a result of these statistical studies, the author concludes that there has been a very marked increase in the death rate from cancer in persons over forty years of age from each of these states. The author points out, however, that a considerable amount of this increase is due to the greater exactitude than formerly with which medical men are now turning in their death certificates, and that the terms "indefinite cause" and "senility," which were used many years ago, have been replaced by definite diagnoses. He thinks that about 30 per cent of the increase may be accounted for by the greater precision and accuracy in the filling out of the death returns. It might be interesting to note that the greatest percentage of increase has been in cancer of the buccal cavity, and the peritoneum, intestines and rectum. Cancer in these two sites shows over 100 per cent increase. Cancer of the female breast shows an increase of 82.6 per cent. This is a peculiarly disturbing observation, as the death rate of these cancers of accessible sites, the buccal cavity and the breast, would certainly have shown material improvement if the efforts to instruct the laity, and the medical profession, in the importance of the early diagnosis of cancer had been successful. Cancer in sites that are not accessible, such as the stomach and liver, show only a 50 per cent increase in the past fifty years. The only decrease has been in the sites which are specified by the Census Bureau as "cancers of other organs or organs not specified," which includes the larynx, lungs, pancreas, kidneys, bladder, brain, bones and other less frequently attacked organs.

The Nature, Incidence and Treatment of Endamebiasis.—A very interesting statistical study of the disease, amebiasis, has been published by BROWN (*J. Am. Med. Assn.*, 1926, **86**, 457), in which he details the study of a large number of cases. It is particularly interesting to note that the large majority of these cases come from the northwestern states of this country. This observation shows very definitely that endamebiasis should not be considered as a disease peculiar to tropics or subtropics. On the contrary, it is a disease essentially of any zone or any climate. A great deal of interest has been aroused the last few years by the publication of reports of the use of different types of drugs in the treatment of amebic infestation. The author has used the alkaloid of ipecac, emetin, in the majority of his cases, and he finds that in conjunction with the use of emetin that

arsphenamin is a valuable adjunct. He calls attention to the fact that this disease is essentially chronic and it is difficult to eradicate parasites. However, if the treatment is persisted in, and the patient is carefully followed over a comparatively long period, eventual cure is not an impossibility. Some protozoölogists are in accord with this statement, while others feel that many cases exist in which it is impossible to eradicate Endameba histolytica from the bile passages if not from the intestinal tract. There is one other point brought out in this paper which deserves to be accentuated, and that is the fact that it is impossible to differentiate between amebic ulcerative colitis and idiopathic ulcerative colitis without a proctoscopic examination. It may be that the incidence of amebiasis in the north would be greater were this method carried out as frequently as it is in the south, where amebic colitis is recognized with great frequency.

SURGERY

UNDER THE CHARGE OF

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The Orthopedic Aspects of Chronic Arthritis.—Osgood (*J. Bone and Joint Surg.*, 1926, **8**, 1) states that rheumatoid arthritis is a disease in which no specific organism has been found which can be held constantly responsible for its causation. Probably many different types of organisms and many other factors play etiologic parts in its onset and course. In the early stages of rheumatoid arthritis, if these organisms and if the other factors can be overcome, complete recovery is possible. In the later stages, if the factors inimical to normal vitality can be eliminated and the essentials for normal body mechanics can be satisfied, arrest of the disease and great functional betterment may be expected. In this stage the simple eradication of a possible surgical focus of infection will rarely be successful in controlling the progress of the disease. Osteoarthritis is a disease in which no specific organism has been conclusively proved to be responsible for its causation. On the basis of the present evidence, its manifestations may occur unassociated with any demonstrable remote or local focus of infection. In the early stages of osteoarthritis if a faulty body chemistry and a faulty body mechanics can be connected and intra-articular friction can be lessened, almost complete relief of the subjective symptoms is possible. In the later stages, if intelligent physiotherapy, protective appliances and well-conceived orthopedic surgery be added to these measures, relief of discomfort and greatly improved function may be expected.

Observations in the Treatment of Gall Stones.—DIGBY (*Ann. Surg.* 1926, **83**, 47) declares that operation should be undertaken at once, as soon as a reasonably probable diagnosis of gall stones has been reached. Very free exposure of the biliary tract is desirable, preferably an angled incision such as Perthes' incision. The bile duct should be opened just above the duodenum as a routine measure and the main ducts very thoroughly explored from within as well as from without. The removal of the gall bladder and cystic duct should generally, though not invariably, be practised, the use of a metal T-tube protecting the main ducts from risk of injury.

Errors in the Interpretations of Urographic Findings.—BRAASCH, (*J. Urol.*, 1925, **14**, 631) believes that the present widespread employment of urography as an aid in the diagnosis of surgical conditions affecting the urinary tract, merits careful consideration of its limitations. Although the deformities seen with various lesions of the kidney and ureter are usually peculiar to the various diseases, nevertheless the various types of pelvic deformity may so closely resemble one another, that their differentiation may be difficult. It is only when the pelvic deformity is definite and typical of a certain type of disease that diagnosis is advisable. It is not apparently known that the normal pelvic outline has many variations and unless one is thoroughly familiar with all the possible variations, he of course cannot recognize deformity. Elongation of one or more of the calices may be so extensive that it is highly suggestive of neoplasm. In doubtful cases a pyelogram of the other kidney made subsequently, may be of value in doubtful cases since the outlines of both pelves are usually more or less symmetrical. Incomplete filling of the pelvis and calices is a frequent source of error in interpretation. Unless the outline is complete the apparent deformity may be taken for neoplasm, cortical necrosis and so forth. On the other hand as the result of insufficient distension hydronephrosis, anomaly and other lesions may easily be overlooked. Another factor which should be considered in interpretation is the effect of previous operation. Correct interpretation of the ureter is particularly difficult. Irregularities in the outline of the ureter have been variously interpreted and the diagnosis of stricture, kinks and pathologic irregularities has been made with comparatively little accurate basis for such interpretation. The elasticity and distensibility of the ureter is apparently not generally recognized. Another element not generally recognized is the spasticity of the ureter. The recognition of renal neoplasm offers one of the most difficult problems in pyelographic interpretation. The main point of differentiation of neoplasm from polycystic kidney is that pelvic deformity in the latter is bilateral.

Surgical Aspects of the Sympathetic Nervous System in the Work of Rene Leriche.—PENFIELD (*Bull. Johns Hopkins Hosp.*, 1925, **37**, 369) says that Leriche has pointed out that in certain pathological conditions of the extremities, the removal of the adventitial coat of the main artery of supply is followed by relief of symptoms. For justification of the operation he relies on the results rather than on a complete theoretical explanation. The cases in which relief is experienced are roughly of two main types. The first group have a circulatory disturbance due

to reflex arterial spasm. It must not be expected that the operation will restore previously obliterated vascular channels. The second condition is causalgia or painful stumps. It might be possible to speak of a third group which would include the so-called trophic ulcers and certain ill-defined skin diseases. Due to his work the nature of the changes after arterial ligation and periarterial sympathectomy are made clear. In spinal anesthesia he has pointed out the probable role of paralysis of the vascular sympathetic fibers proceeding from the thoracic segments of the cord in causing the dangerous reactions to that form of anesthesia.

THERAPEUTICS

UNDER THE CHARGE OF
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Treatment of Effusions in Artificial Pneumothorax.—HUDSON (*Brit. Med. J.*, 1925, ii, 1125) bases the treatment of effusions in artificial pneumothorax on the three distinct forms in which it may appear, that is: (1) Simple, (2) serous and (3) purulent. In at least 50 per cent of the cases a simple effusion follows artificial pneumothorax, and as it causes no symptoms, it requires no treatment. Serous effusion is also a frequent complication, but the fluid should not be aspirated unless it persists after a long period, in spite of repeated sweating; in any case replacement with air is necessary to prevent reëxpansion of the lung and adhesions. Purulent effusions, Hudson divided into three classes. The first is due to infection with the tubercle bacillus alone. When all active symptoms have subsided he advises withdrawal of the fluid at weekly intervals, followed by replacement with air until the chest is emptied. The second group, which is due to a mixed infection with tubercle bacilli present also, he advises, the same procedure, and in some instances instead of replacing with air he replaces by oil of gomenol (10 per cent), which seems to prevent reaccumulation of pus. The third group consists of those cases of acute massive secondary infection of the pleural cavity with high fever of a septic type, rapid emaciation and all the other signs of acute septic poisoning. In such cases the pleura must be drained, and, if possible, a plastic operation is performed at a later date. These cases are very often fatal.

Discussion of the Treatment of Asthma.—BROWN (*Brit. Med. J.*, 1925, ii, 366) summarizes the treatment of asthma and emphasizes particularly the psychic factor and the necessity of restoring the balance in favor of the sympathetic nervous system. Peripheral stimuli from the respiratory, gastrointestinal and genital tract are generally recognized as important causes of asthma, but he particularly emphasizes enlarged bronchial glands as an important cause in children. Sensitization to foreign proteins is well recognized in asthmatics, but they

often do not react to that specific foreign protein which may excite an attack. On the other hand, if a foreign protein is really toxic it may provoke a reaction in anyone, and severe bacterial infections of the upper respiratory tract which, by lowering the resistance, may produce a sensitiveness resulting in asthma. The toxins of syphilis in late adult life may also produce the same result. Patients with asthma being recognized to be vagotonics, one would expect those to be glands of internal secretion which coöperate with the sympathetic to help in checking an attack, that is, the thyroid, adrenals and posterior pituitary glands. Therefore, when the endocrine balance sways in the direction of the vagus asthma is likely to occur in susceptible persons. The suggestibility of each patient may be used in treating a case of asthma, and a search made to find any psychologic troubles. Desensitization may be used not only with those who are sensitive to foreign proteins, but in many cases nonspecific treatment may also be successful. Desensitization during freedom from attacks at high altitudes may be successful. Belladonna is effective because of its paralyzing effect on the parasympathetic nerve endings, just as adrenalin and cocain are effective for their action on the sympathetic. Iodin is believed to activate the thyroid, and its benefit may thus be due to the effect of thyroid secretion in lowering the threshold of stimulation of the sympathetic.

Discussion on the Treatment of Chronic Arthritis.—In a discussion of the treatment of chronic arthritis HORDER (*Brit. Med. J.*, 1925, ii, 633) emphasizes the fact that chronic arthritis is a general disease with local manifestations, and, although the infective factor is present to some extent in almost all cases, its manner of operation is often very difficult to elucidate. Arthritis as a definite expression of focal sepsis forms an intermediate group between the cases of direct joint infection, and those termed "rheumatoid," which, owing to our ignorance of the degree to which the element of infection is present, form the crux of the therapeutic problem. In the treatment of this intermediate group drainage of the area of focal infection is the first step, but no area should be condemned before the whole field is investigated. Teeth and tonsils or teeth and gastrointestinal tract are often all involved. One focus of infection at a time should be eradicated, and after a suitable interval the remaining foci. The prostate and the uterus are both capable of causing chronic arthritis without definite evidence of bacterial infection. The intestinal tract, and particularly the colon, may be the source of the toxemia, and in cases where bacterial evidence is lacking treatment may be based on the fact that the streptococcus, both hemolytic and nonhemolytic, are the usual microorganisms concerned in the infective element in arthritis. Antigen therapy should be supplementary to drainage of the infected area, not a substitute for it. In treating intestinal cases the author believes that the diet, with a view of lowering the bacterial content and mechanical cleansing, is more important than "intestinal antiseptics." However, mercury and salol he advises when the latter are indicated. As in any chronic infection, a healthy hygiene is most important. In chronic arthritis few endocrine disturbances are found which would indicate the necessity of giving extracts of the glands of internal secretion, but thyroid gland in small doses if often helpful, particularly in the

older patients. The importance of the metabolic factor is difficult to determine, but gout may often be combined with an infective process and should be treated with alkalies, colchicum or atophan, depending on the degree of symptoms. For effusions into a joint the author recommends tincture of iodin in the form of the French codex preparation, and gives 1 minim a day, increasing 1 minim daily until the patient is taking 30 minims a day. To control pain he prescribes aspirin, pyramidon or codein. The latter should only be used in exceptional cases and combined with aspirin and caffein. Spa treatment he approves of, because of the benefit derived by patients whose nutrition, nerves and general metabolism need improvement. In treating the joints locally one must first of all get the confidence of the patient, for restoration of function by mechanical, thermal or electrical measures is never as successful as active measures which the patient himself can make if encouraged, and he should realize that every effort he makes to restore and improve the function of diseased joints reacts beneficially on the disease itself.

PEDIATRICS

UNDER THE CHARGE OF

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Etiology of Tetany.—LESNE and TURPIN (*Presse med.*, 1926, **34**, 1) say that the spasm in tetany seems to be a syndrome of exaggerated neuromuscular excitability, in connection with the transient humoral changes. The chronaxia of the nerve and muscle shows that the changes are similar to those induced by vasomotor disturbances, by chilling or brief intoxications. A reduction in calcium ions appeared to be associated with disturbances of the acid-base balance of the plasma in their patients. This humoral syndrome corresponds to that described by Bigwood in epilepsy. It is probable that the acid-base imbalance affects not only the nervous system, but also the tissue of ectodermal origin. The function of organs controlling the carbohydrate or protein metabolism may also be involved. The theories which ascribe spasmophilia to the parathyroids, to the action of toxins or to an excess of deficit of calcium do not necessarily conflict, but lack of calcium ions seems to have the surest foundation of them all as the main factor in tetany.

Hemorrhagic Measles with Encephalitis.—LOWENBURG and SCHALLER (*Arch. Pediat.*, 1926, **43**, 73) report an interesting case. They say that, while comparatively rare, encephalitis occurs as a complication and as a sequel of measles. Convulsions, coma, paresis, loss of speech or impairment or loss of any of the higher senses, occurring during measles and extending into and beyond the period of convalescence, should rightly be regarded as evidences of infections or toxic inflam-

matory change in the brain or its membranes, such as an encephalitis. This condition is more common in the hemorrhagic type of measles, and whenever suspected lumbar punctures should be done. Encephalitis occurring in measles may proceed at full recovery. The efficiency of convalescent measles serum, injected intra-spinally, intravenously and intramuscularly in encephalitis complicating measles has not been proved, but is worthy of further trial. It produces no reaction of anaphylaxis and is entirely harmless. It should be used early, preferably as soon as symptoms, proven by lumbar puncture, indicate involvement of the brain and its membranes. The dosage must be large.

Wheal Formation in Infants and in Children.—PILCHER (*Am. J. Dis. Child.*, 1926, **31**, 77) defines wheal formation in the skin as a manifestation of increased permeability and dilatation of the minute vessels. The author made a study of wheal formation by the intradermal injection of codein solution in a series of normal and sick infants and children. He found that wheal formation was lessened in all cases of edema studied, regardless of the cause, such as nephritis, cardiac decompensation, leukemia, malnutrition from starch-feeding injury and in the local skin edema of serum urticarial wheals and saline infusions. This result is due to the edema of the skin diseases, and not to decreased vessel permeability. Wheal formation is also lessened in certain ill-defined skin infiltrations, such as cretinism and myxedema and sclerema and sclerederma. In nephritis without edema the wheal formation, and consequently the vessel permeability, is normal, indicating that the cause of edema in nephritis is not increased vascular permeability. In valvular and congenital heart disease without edema, even with considerable decompensation, the wheal formation is normal, indicating an efficient circulation in the skin. In myocardial degeneration and in certain cases of severe prostration wheal formation is diminished because of the lessened circulation in the skin. A normal wheal reaction indicates an efficient circulation at the site of the wheal. The presence of a strongly positive tuberculin reaction does not modify wheal formation.

Diphtheria following Tonsillectomy.—ZINGHER (*Am. J. Dis. Child.*, 1926, **31**, 72) emphasizes the advisability of preliminary nose and throat cultures for diphtheria bacilli as a routine procedure before such operations as tonsillectomy and adenoidectomy. If the cultures are positive a prophylactic dose of 1500 units of diphtheria antitoxin should be injected, unless the patient has already been tested with the Schick test and shows a definite negative or a negative pseudoreaction. If the patient is a carrier who is to be treated by the removal of tonsils and adenoids, it is especially important to make certain that there is a negative Schick reaction or, if a positive reaction is present, that a prophylactic dose of diphtheria antitoxin be given. Infection with the diphtheria bacillus and development of the disease clinically may occur a week or two after tonsillectomy, and before the operative wound has completely healed. Preliminary throat cultures in these cases would be negative for the Klebs-Loeffler bacillus. The surest safeguard against diphtheria as an operative complication in nose and throat surgery would be active immunization of all young children with

the new one-tenth L+ mixture of toxin antitoxin or with diphtheria toxoid. The antitoxin immunity thus established would protect the person to be operated upon against local infection with the diphtheria bacillus and systemic intoxication with its toxin. The intact normal mucous membrane of the nasopharynx has a definite local resistance which protects persons who have no general antitoxic or antibacterial immunity against such pathogenic bacteria, the diphtheria and scarlet fever organisms and their toxins. The nature of this local resistance is not yet definitely known. It may be readily destroyed by an operative procedure, such as tonsillectomy, or by an inflammatory process, such as a cold, an attack of scarlet fever or of diphtheria. The periods of incubation, as usually understood by general practitioners and health officers, hold good only under conditions in which the infecting organism or virus is highly virulent for the human race, and in which the normal mucous membrane presents no barrier to invasion. Such is the case with measles where the period of incubation is quite definite. In other diseases, such as diphtheria and scarlet fever, which are not highly infectious for man, the period of incubation depends to a greater extent on the interplay of factors, such as the local resistance of the mucous membrane, the variable virulence of the infectious agent and the general specific resistance of the individual. The periods of incubation in these two diseases may be extended, the final development of the disease in a susceptible person depending on some factor such as trauma or infection, which destroys local resistance of the intact mucous membrane and with it the nonspecific protection of the patient.

Irradiation of Foodstuffs with Ultraviolet Light—MACKAY and SHAW (*Lancet*, 1926, i, 8) studied the clinical value of certain irradiated foodstuffs in the treatment of rachitic children. Three children received irradiated dried milk. In 1 case the milk formed only part of a mixed diet, which included meat and vegetables. All 3 children showed roentgen-ray evidence of healing between the fifteenth and twenty-second day after the beginning of treatment, and in all there was steady progress in calcification. This was at a rate comparable to that usually obtained by direct exposure of the child to the light of the lamp or by administration of cod liver oil by mouth. In 1 child suffering from spasmophilia the condition was cured in just the same manner as it would have been by direct irradiation. In order to test whether or not the antirachitic property induced by light in the milk would withstand the effects of cooking, 2 children were given irradiated dried milk, which, after being mixed with water, was simmered over a gas flame, the temperature being kept at boiling point ten minutes. Both these children had passed through a preliminary control period period during which there was no evidence of healing. The Roentgen ray showed the first evidence of healing on the seventeenth and nineteenth day, respectively, after the boiled irradiated milk was first given. One child with severe rickets received irradiated full-cream sweetened condensed milk in place of dried milk. The same rapid calcification was brought about as in the other 5 cases. The results obtained with irradiated white wheaten flour was inconclusive and probably negative. They gave irradiated cottonseed oil to only 1 patient. In this case healing was apparent on the thirty-ninth day and progress in calcification was slow.

DERMATOLOGY AND SYPHILIS

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Lacquer Dermatitis Treated with Rhus Toxicodendron Antigen.—WILLIAMS (*Arch. Dermat. and Syph.*, 1925, **12**, 851) reports a case of lacquer dermatitis in a trained nurse, aged thirty-two years, occurring on the right arm from the wearing of a lacquered bracelet and presenting the picture of a typical rhus poisoning. She had been subject to attacks of ivy poisoning since childhood, each time being incapacitated for several weeks at a time. On three successive days she received an intramuscular injection of rhus toxicodendron antigen, and made a very rapid recovery, improvement being especially notable after the last injection. The author knows of no other report of the treatment of lacquer dermatitis with rhus toxicodendron antigen and believes that it may be useful in any form of rhus poisoning.

Use of Tryparsamid in Patients With and Without Ocular Lesions.—CADY and ALVIS (*J. Am. Med. Assn.*, 1926, **86**, 184) divided their 180 patients into two classes: (1) 153 called normal, that is, having no recognizable signs of optic neuritis or atrophy, loss of visual acuity, or contraction of visual fields; (2) 27 abnormal, because of the presence of one or more of the foregoing signs of optic involvement. The usual routine of treatment consisted of 50 mg. of tryparsamid per kilogram of body weight once weekly, and mercuric salicylate in 0.06 gm. doses, three or four days after the tryparsamid injections, for a period of eight weeks, when a rest period of from four to six weeks was allowed. Treatment was altered to conform with any visual disturbances, to suit the tolerance of the patient generally or to suit his special needs. Of the 153 normal patients only 8, or 5.2 per cent, had sufficient manifestations to alter treatment. Among these 8, 3 had only a slight contraction of the visual fields which disappeared after temporary withdrawl of the treatment; 5 had marked constriction, of which 2 (1.3 per cent) failed to improve, hence apparently injured by the use of tryparsamid. Therefore, the percentage of normal patients that had permanent visual impairment is so low that it falls far short of being a serious contraindication to tryparsamid as another weapon against syphilis. The consideration of those already showing ocular involvement who were objectively damaged is a serious one, as 10 out of the 27 abnormal patients (37 per cent) became definitely worse, the remainder showing moderate or no improvement. However, this 63 per cent who either had the eye condition arrested or improved is a note-

worthy feature when one considers the usual unfavorable outlook for such ocular lesions. The authors conclude that tryparsamid can be used by experienced persons with comparative safety on patients having normal optic tracts; patients with optic involvement, such as contracted fields or abnormal fundi, are more liable to injury by the treatment than normal patients, but show favorable response to treatment if it is properly controlled; important subjective signs of adverse action of the drug on the optic tract are dimness of vision, flickering sensations or flashes of light; objective findings, as diminution in the visual acuity, contraction of the visual fields or changes in the fundi, call for an immediate suspension of tryparsamid for at least one month, when it may usually be resumed.

Interstitial Keratitis.—In order especially to determine the effect of thorough antisyphilitic treatment on interstitial keratitis, CARVILL and DERBY (*Trans. Sect. Ophthal., J. Am. Med. Assn.*, 1925) compared 100 cases treated intensively to 100 cases which were seen previous to 1910, prior to the advent of arsphenamin. The 100 treated cases were selected from 222, the cases chosen for comparison being those in which the longest time had elapsed from the subsidence of the acute symptoms of the interstitial keratitis to the final examination, and whose treatment might be considered intensive according to modern standards. The treatment for syphilis consisted of numerous injections of the arsphenamins, mercurials by injection, inunction, and by mouth, in addition to iodids when indicted. Except for the shorter periods of observation of these "treated" cases, a fair comparison can be made. In the series of "untreated" cases none of them had received arsphenamin or its allied preparations or injections of mercury. Such treatment as they had received had been over comparatively short periods of time or none worthy of mention. In a general study of the 322 cases, the greatest incidence occurred between the ages of five and ten years. The ratio of females to males was approximately 3 to 2. The blood Wassermann was positive in 98 per cent, and collateral evidence of syphilis was present in 78 per cent. In the usual untreated case the second eye is generally involved to the same degree as the other eye, but the course of the disease is shorter. In the effectively treated cases which received arsphenamin 19 per cent entirely escaped involvement of the second eye, and in 36 per cent the involvement of the second eye was less severe than the first. This is a notable gain over the course in less effectively treated cases. Of the poorly treated or untreated cases 27 per cent relapsed; while in the energetically treated cases relapse occurred in only 3.6 per cent. Later syphilitic involvements, such as deafness, synovitis, aortitis and so forth occurred in 23 per cent of the untreated, while in the treated later specific accidents occurred in 11 per cent. It is extremely difficult, perhaps impossible, to prevent the development of interstitial keratitis by the use of antisyphilitic treatment in earlier life. Really intensive modern treatment will, however, prevent relapses in a striking proportion of patients and involvement of the second eye prevented or made less severe in more than 55 per cent.

Clinical and Serologic Value of the Colloidal-benzoin Reaction.—OSBORNE (*Arch. Dermat. and Syph.*, 1925, **12**, 706) justly advocates the urgent need of a simple, inexpensive and reliable serologic test to differentiate general paresis, and especially incipient general paresis, from other forms of neurosyphilis. The colloidal benzoin reaction of the spinal fluid seems more nearly to fulfill these requirements than either the colloidal-gold or the gum-mastic tests. The mastic test has not come into such wide usage as the colloidal-gold reaction, and is generally rated less sensitive and of much less value in diagnosis than colloidal-gold test. In an extensive review of the literature the author found the results secured in the colloidal-gold test to vary widely by the various workers; although it is of value in many cases, it is open to too many errors and the results lack uniformity and reliability. In order to estimate the clinical and serologic value of the colloidal-benzoin test, 2045 complete and 617 modified tests were made on the same spinal fluids, using the exact technique as advocated by Guillain, Laroche and Lechelle, the originators of the test. Judging by the results of this number of tests on 192 patients, of which 153 had neurosyphilis in some form and 39 had various neurologic conditions other than syphilis, the colloidal-benzoin test is superior to the colloidal-gold in its ease of performance, uniformity of result, reliability and amount of information furnished. There is a great deal of evidence that precipitation in the first zone is an index of the degree of active involvement of the parenchyma of the brain, and that purely vascular, meningeal or spinal-cord lesions produce precipitation in the second zone. The author's series did not support the view of the originators of the test, that the colloidal-benzoin reaction is specific for neurosyphilis in the sense that the spinal fluid Wassermann is. The author feels that the colloidal-benzoin test should have a wide field of usefulness in differentiating general paresis from other forms of neurosyphilis.

Fusiform Bacilli and Spirochetes.—PILOT and MEYER (*Arch. Dermat. and Syph.*, 1925, **12**, 837) report an unusual case of a colored male, aged twenty-eight years, with a gangrenous infection of the finger, caused by fusiform bacilli and spirochetes resulting from injury inflicted by teeth of an opponent in a fight. In their previous studies they had pointed out that the putrid infections were often caused by these anaërobes, and their source was related to the distribution of these bacteria on the human body. When the above patient was seen after three weeks had elapsed the terminal phalanx of the finger had a deep necrotic ulceration, discharging a thick, purulent material; no adenopathy was palpable. Smears of the pus stained with 10 per cent carbol fuchsin show the organisms mentioned. Amputation of the hanging phalanx and two doses of 0.6 gm. neoarsphenamin completely healed the ulceration. This finger lesion is of great interest because it illustrates the pathogenicity of the anaërobes formed in the discharge. The destructive character, the putridity of the ulcer and the response to neoarsphenamin is similar to that observed in lesions associated with fusiform bacilli and spirochetes in ulcerative stomatitis, gangrenous balanitis and pulmonary abscess and gangrene.

OBSTETRICS

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Maternal Mortality in Massachusetts.—COFFIN, DEKRUIF, SOUTHARD and HAMBLEN (*J. Am. Med. Assn.*, 1926, **86**, 408) present a series of 984 deaths occurring in Massachusetts during 1922 and 1923 among women from the sixth month of pregnancy through the first month of puerperium from causes immediately related to pregnancy or childbirth or from causes in which pregnancy or childbirth was a controlling factor. Their report comprises charts and twenty-two tables from which they draw the conclusions that poverty as a factor of maternal mortality was negligible, that 89 per cent of the cases lacked adequate prenatal care, and that so-called preventable causes, as septicemia, toxemia and hemorrhage were responsible for 58 per cent of the deaths.

Influence of Pregnancy on Blood Lipoids.—TYLER and UNDERHILL (*J. Biol. Chem.*, 1925, **66**, 1; Abstract, *J. Am. Med. Assn.*, 1926, **86**, 447) found the total ether extract of whole blood in pregnant women from the third month of pregnancy to term to be higher than in the non-pregnant. The average value in 11 cases studied is roughly 30 per cent higher at three months and 50 per cent higher at term.

The Effect of Gas Anesthesia Used in Labor on the Bleeding and Coagulation Time of the Newborn.—SANFORD (*J. Am. Med. Assn.*, 1926, **86**, 265) studied a large series of cases. This was made possible in the obstetrical department, as both ethylene and nitrous oxide anesthesia were used on different services at the same time. The length of time of the anesthetic given to the mothers was taken into consideration, and no case was considered in the series unless intermittent inhalations of the anesthetic were kept up over thirty minutes. The average length of time of anesthesia in nitrous oxide cases was one hour and forty-nine minutes and of ethylene gas one hour and fifty-four minutes. The coagulation and bleeding times were taken of each child born in the department at birth and once again during the first ten days. Rudolph's method with slight modification was used throughout for the coagulation time. The bleeding time was by the Duke method. The results obtained were most instructive, yet did not show any pronounced or prolonged coagulation or bleeding time to a dangerous limit, all returning to the normal at the end of nine days. Of the cases which received no anesthetic the bleeding time was less than

those children whose mothers received either anesthetic during the second stage of labor, and at the end of the sixth day the bleeding time of those whose mothers did receive either nitrous oxide or ethylene were the same. The coagulation time was less in the babies born of mothers which did not receive an anesthetic, up to the ninth day when they again were all alike. In the nitrous oxide cases there was a definite prolongation of the bleeding time of one minute at birth and two minutes' coagulation over the nonanesthetized mother's offspring. In the ethylene series there was a definite prolongation of the bleeding time of two minutes at birth and the coagulation time of three minutes. All cases were the same at the end of the ninth day of life regardless as to whether an anesthetic was administered or not.

Report of a Case of Separation of the Dorsal Vertebræ in Podalic Version and Extraction.—BARNEY (*Am. J. Obst. and Gynec.*, 1926, **10**, 116) reports a case in which there was a separation of the fourth and fifth dorsal vertebræ with no fracture occurring during operative delivery in which no undue force was used. He believes that there was an inherent weakness in the union of the fourth and fifth dorsal vertebræ which caused this accident. The child was delivered by podalic version and extraction.

Obstetric Mortality: Analysis of the Cases at the Lying-In Hospital, New York, during 1924.—ROSENSOHN concludes, from the figures gathered, that we should concentrate more on the full-term fetuses, by watching for abnormalities; not to permit a woman who has gone through more or less distress for ten months to have a stillborn baby because interference was not instituted until too late. The fetus should be observed closely for signs of distress as evidenced by the passage of meconium, turbulent movements or by rising, slowing or irregularities of the heart. The obstetrician should interfere and not alone where there is fetal distress, but even before this state is reached.

Application of Forceps to the Transverse Head for Delivery of Persistent Occipitoposterior Cases.—WILSON (*Am. J. Obst. and Gynec.*, 1926, **10**, 37) states that the principle of this procedure is the application of forceps to the head lying in transverse position in the pelvis. In persistent posterior positions the head is rotated to the transverse position manually and the posterior side of the forceps introduced into the brim of the sacrum. The second position (R. O. P. the right blade, in L. O. P. the left), the blade is inserted along the side of the pelvis, the handle depressed and the blade placed on the side of the head beneath the symphysis. Rotation takes place easily. The author calls attention to the fact that rotation should be complete before traction is made. The extraction is the same as in any other anterior head position. His statistics in a large series of cases, both private and hospital work, show very good results. He advises mediolateral episotomy in all these cases. He reports 100 cases with no maternal deaths and no stillbirths.

GYNECOLOGY

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Treatment of Gonorrheal Salpingitis.—For some years much real investigative work in the subject of pelvic infections has been done by CURTIS (*Surg., Gynec. and Obst.*, 1926, **42**, 6), and we have quoted many of his articles in the past. In a recent contribution he discusses the subject of gonorrheal salpingitis from a new angle based upon some of his research work. He states that for some time it has been known that the gonococcus does not live long in the lumen of the tube. It has always been assumed that the bacteria remain viable in the deeper tubal wall and that chronic infection is thus maintained. In a search for dormant infection cultures made of over 200 thoroughly ground Fallopian tubes revealed that it is almost never possible to obtain the gonococcus longer than two weeks after disappearance of fever and leukocytosis. Upon completion of the major portion of this work, in 1921, he came to the conclusion that gonorrheal salpingitis is a self-limited process; persistently active gonorrhea of the tubes appeared ascribable to *recurrence* of infection from without, rather than to chronic infection. Furthermore, it appeared, also, that male carriers are not the only source of tubal reinfections; gonococci remain long viable in the lower genital tract, and fresh infection of the tubes may result from traumatism of the cervix or from the passage of vaginal douches upward through the cervical canal. It had previously been his custom to remove notably diseased tubes of service patients after complete subsidence of acute infection. In 1921 he began to avoid operation. Patients were isolated from their sources of infection, were forbidden to take douches and were treated expectantly. As a result, it was found that those who suffer from only one attack of salpingitis rarely have severe symptoms or reveal extreme pathologic changes. Even those who have been repeatedly infected tend to ultimate recovery if removed from consorts who are carriers of disease. From bacteriologic study combined with five years' conservative clinical experience he has concluded that operation upon Fallopian tubes for eradication of gonorrheal infection is not often indicated. The infection disappears spontaneously if the patient is isolated from the source of her disease. Expectant care eventuates in clinical recovery of the great majority of patients and is beneficial to those who must ultimately obtain operative relief. Surgery should usually be long delayed and reserved chiefly for sequelæ, such as adhesions, menstrual disturbances and sterility. To those who would ask whether operation is not always indicated in patients with a history of repeated attacks, he would suggest that the most satisfactory management is

"conservatism;" such, for example, as a gynecologist of today might observe in the care of his sister before resorting to surgical intervention. It may be thought that woman cannot be persuaded to abstain from exposure to repeated infection. This is seldom true. The difficulty lies in the fact that we have overestimated the persistence of a single infection and have not sufficiently emphasized the danger of subsequent exposure. When a sufferer from salpingitis is frankly informed that she must choose between prolonged abstinence and surgical removal of the genitalia, conservatism wins. (Occasional indulgence, later, with sheath protection, is a helpful compromise measure.)

Treatment of Ovarian Hemorrhage with Ovarian Transplants.—One of the most trying and at times serious conditions which the gynecologist is called upon to handle in young patients is that condition which causes severe uterine hemorrhage at the time of the menstrual periods and which is thought to be due to some form of ovarian dysfunction. In the past these cases have been treated by means of medicines and glandular therapy with more or less success, and latterly small doses of radium have proved to be quite successful. An article dealing with this subject, and recommending treatment by means of homotransplants of human ovaries, has been presented by SIPPEL (*Zentralbl. f. Gynäk.*, 1926, **50**, 99), based upon his experiences in 20 cases. In treating these patients he usually performs a diagnostic curettage followed by an abdominal section with the correction of any pelvic abnormality, such as uterine retroversion or any adnexal disease, and at the time of closing the incision he transplants a few small pieces of ovary which have very recently been removed from another patient. He states that the results have been most satisfactory, and that the alarming menorrhagia usually disappears almost at once. It is of interest to note that he has found that before the operation the mucous membrane of the uterus has often been found to be functionless, containing no glycogen, whereas, after the transplantation of the ovarian tissue glycogen is found to be present in the ovarian mucosa. We quote this article merely to call attention to the type of work that is being done in Germany at the present time, but do not recommend it because we have found that the judicious use of small doses of radium will practically always control this type of hemorrhage without the dangers of the abdominal section. Furthermore, in some of the cases quoted the ovarian transplants were taken from patients in whom a radical extirpation of the uterus was done for carcinoma of the cervix, and it seems to us that the use of ovarian tissue from such a patient for transplant purposes is certainly not justifiable.

Blood Sedimentation Test.—On several previous occasions we have abstracted articles on the blood sedimentation test especially as it relates to the diagnosis of pelvic disease, most of the articles presented being rather enthusiastic as to its diagnostic virtues. In a recent article CHERRY (*Am. J. Obst. and Gynec.*, 1926, **10**, 105) states that the sedimentation time of the blood is a simple test, readily performed is unquestionably true. The rate of sedimentation, however, is easily influenced in diseases by absorption into the general circulation of unknown substances that produce a change in the chemical and physi-

cal balance of the blood elements. This balance is no doubt readily upset, and this is especially so in all types of infection, thus rendering it a most delicate indication of the invasion of the human organism by disease. This is manifested by an increase in the speed of settling of the red blood cells, that responds to infection much more quickly than the increase in the number of leukocytes. The increased rate of sedimentation does not, however, indicate the degree and virulence of the infection, as shown in the 71 cases of adnexal infection reported in this article; neither from the observations made, does a low sedimentation time signify a bad prognosis. However, a steady lowering of the time means an increasing toxemia that may terminate fatally, yet it would be unwise to base a prognosis upon this one test unless substantiated by other reliable clinical manifestations. As a diagnostic agent alone, it is untrustworthy in pelvic conditions, yet it may aid in influencing an already doubtful position to one that is more tenable. In pelvic infections the leukocyte count, while not so readily affected or delicately influenced as the sedimentation time, is for this reason a more reliable indicator of the degree and virulence of the infecting organism, and, therefore, more dependable as a means to determine the most suitable time to interfere surgically.

OTO-RHINO-LARYNGOLOGY

UNDER THE CHARGE OF

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Ephedrin Sulphate, the Alkaloid of Ma Huang—Effects of Local Applications on the Nasal Mucous Membrane: Preliminary Report.—Ephedrin is the active principle of the Chinese drug, ma huang. Experiments on dogs, cats and rabbits have shown uniformly that the effects of ephedrin on circulation, smooth muscle and secretions are analogous to those of sympathetic stimulation and are qualitatively similar to those of epinephrin. As one phase of a clinical study of the effects of ephedrin sulphate, FETTEROLF and SPONSLER (*Arch. Otolaryngol.*, 1925, **2**, 132) employed a 5 per cent solution on the nasal mucous membranes of 17 patients who had turgescence of the nasal mucosa. The color and contour of the nasal mucous membrane, particularly of the inferior turbinates, were first observed and recorded. The distance of the mesial surface of the turbinate from the septum was likewise measured and recorded. With a cotton brush the drug was then lightly painted over the anterior part of the lower turbinate of one side of the nose only for an area of about 1 cm. in diameter. After application the turbinate was observed frequently during the ensuing ten minutes, at hourly intervals for six successive hours and finally at the end of twenty-four hours and comparisons made with the opposite, untreated side. It was found that contraction of the turbinal mucosa began in from a

few seconds to one minute after application, that the contraction proceeded with marked rapidity, its maximum being established in from one and one-quarter to five minutes, with an average of two and one-third minutes; that relaxation began after a period of two hours and thirty-five minutes, on an average, and was complete in the average time of three hours and seventeen minutes. There was no sign of irritation of the mucous membrane. In other words, ephedrin sulphate seemed to possess all the advantages of epinephrin and perhaps none of the disadvantages.

Dynamic Studies on the Cerebrospinal Fluid in the Differential Diagnosis of Lateral Sinus Thrombosis.—"Increased intracranial pressure is normally propagated throughout the cerebrospinal fluid system and may be measured by a manometer employed in connection with lumbar puncture. Compression of the internal jugular veins causes increased intracranial pressure with immediate rise in spinal-fluid pressure. It is now generally considered that absence of rise in fluid pressure on jugular compression (positive Queckenstedt sign) indicates spinal subarachnoid block, a most important and early sign in spinal-cord tumor. It may be safely said that the criteria on which these tests depend and the results of the tests have been for the most part dependable. So much so, in fact, that the effect of jugular compression on spinal-fluid pressure now forms one of the routine tests in diagnostic lumbar puncture." Recognizing that the mechanism is different, TOBEY and AYER (*Arch. Otolaryngol.*, 1925, **2**, 50) utilized this test in the diagnosis of lateral sinus thrombosis, where the absence of rise in pressure in the spinal-fluid manometer is not due to obstruction of the fluid, but to venous obliteration. With the patient in the lateral position, lumbar puncture is performed and the fluid is permitted to run into a glass manometer of 2-mm. bore. After the initial pressure reading, digital compression of one, and then the other, internal jugular vein is made, noting the rapidity of rise of the fluid column in the manometer. Then, for comparison, both sides of the neck are compressed simultaneously. In a typical case of lateral sinus thrombosis there is a prompt and rapid rise in fluid pressure to twice or three times the intial reading when the internal jugular vein draining the normal sinus is compressed. This pressure rise is maximal, being equivalent to the pressure attained when both jugular veins are compressed. Pressure over the vein draining the thrombosed lateral sinus causes either no rise or, more commonly, a slow rise of only from 10 to 20 mm. in the manometer. After having performed over 3000 punctures in cases in the neurologic clinic, the authors caution as to such pitfalls of technique as abnormally low tension of the spinal fluid, persons with thick necks, abnormal rise in fluid pressure due to carelessness, normal difference on the two sides and anatomic variation in the size of the lateral sinuses. They also recognize two known dangers: (1) Sudden death following lumbar puncture from the presence of subtentorial abscess or tumor; (2) the precipitation of acute meningitis, although in 20 cases of lateral sinus thrombosis, they have not encountered any evidence of ill effect from the technique.

The Significance and Prevention of Blindness due to Intranasal Disease.—"Blindness and lowering of the visual capacity from disease of the nasal accessory sinuses is far more common than is generally supposed." The cause of retrobulbar neuritis are enumerated by GOTTLIEB (*Laryngoscope*, 1925, **35**, 844) as: (1) Nasal accessory sinus disease, particularly disease of the ethmoid and sphenoid; (2) abscesses at the apices of teeth; (3) far less common, all other causes such as absorption of toxic material from the intestines, inhalation or ingestion of poisons, such as lead, arsenic and acetone, and diseased states, such as syphilis and probably diseased tonsils. After a review of the anatomic relationships of the optic tract and canal with the sphenoidal and ethmoidal sinuses, and presenting clinical data and the results of various sinus operations or individuals with amaurosis, the author concludes that retrobulbar optic neuritis is caused in the great majority of cases by disease of postethmoidal and sphenoidal sinuses; if time permits all other causes should be excluded before operating, but if time is precious one is justified in opening the sinuses without further investigation; negative findings in the nose are the rule rather than the exception; the middle turbinates should not be spared at operation in any instance.

Chemotherapy in Otitis Media.—SCHWARTZ (*Ann. Otol., Rhinol. and Laryngol.*, 1925, **34**, 932) employed several drugs and combinations of drugs in the treatment of acute and chronic otitis media. The method consisted in gaining free access to the tympanic cavity by incising the drum head and irrigating the external auditory canal with half strength hydrogen peroxid. After the external meatus was cleaned and dried a half medicine dropper of meroxyl (sodium hydroxymercuribenzophenone sulphonate) and acetic acid solution was then washed back and forth in the canal. The ear canal was again dried and a few drops of gentian violet and neutral acriflavin combination were instilled into the canal and a piece of cotton placed at the meatus to prevent overflow. The meroxyl acts mainly on Gram-negative organisms, as influenza and colon bacilli; the acetic acid is almost a specific for Bacillus pyocyaneus and the gentian violet—acriflavin (acriviolet) is more germicidal for Gram-positive bacteria, such as streptococci, staphylococci and pneumococci. If smears and cultures were made from the aural pus that drug which acted best on the microörganism found was employed. The author states that the results obtained from this method "have been very good; especially remarkable were the cures obtained in chronic otitis media of months' standing, with a foul odor and a thick pussy discharge." The various dyes—neutral acriflavin, gentian violet, mercurochrome and brilling green—were all made up in 20 per cent alcohol and used in 1 per cent strength. The meroxyl was employed in 0.5 of 1 per cent strength, and was made up in an aqueous solution. The author calls attention to the ease of application of the method, the abolishing of irrigation at home, the shortening of duration of the aural discharges and the lessening of frequency of mastoid complications. The one disadvantage is the staining attendant upon the use of the gentian violet.

RADIOLOGY

UNDER THE CHARGE OF

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The Effect of Exposure to Roentgen Ray on Reproduction in Male Rats.—HOOKER (*Am. J. Roent. and Rad. Ther.*, 1925, **14**, 327), after a thorough and careful study feels that it is quite impossible to foretell with any degree of certainty the effect which will be produced on the reproductive glands. The inability to obtain results of any uniformity, even approximately, indicates an extreme difference in individual resistance not hitherto recognized in studies of this kind.

Report of 1326 Roentgen Examinations for Suspected Urinary Calculi.—WALTON and LUSCINIAN (*Am. J. Roent. and Rad. Ther.*, 1925, **14**, 320). Of 1326 roentgen examinations for suspected urinary calculi, only 16.4 per cent showed positive shadows. Hypertrophic arthritis of the spine gives rise to symptoms simulating those of urinary calculi. Calculi were more frequent on the right side in this series. Pyelograms showed hydronephrosis and hydroureter to be far more common on the right side. Gall stone attacks may simulate renal colic. The majority of the renal calculi were small, less than 1 cm. in diameter.

Results of Roentgen Ray Therapy for Uterine Cancer: Statistical Report of 800 Cases.—WINTZ (*Radiology*, 1925, **5**, 500) gives an extended report of his results since 1915. Cures are classified as provisional, relative and absolute, and the cases are grouped into operable and inoperable. In the class of "absolute" cures he includes those patients who are living five years after treatment. The percentage of absolute cures varies among the years during which treatment was given; the maximum was 21.2 per cent of those treated in 1920. He concludes that the efficacy of roentgenologic treatment depends on many factors, including technical thoroughness, the kind, quality, location and extent of the tumor, the general living conditions of the patient, and the "retrogressive ability" of the tumor.

Cholecystography: Observations on the Oral Administration of Sodium Tetrabromphenolphthalein.—LARIMORE (*Radiology*, 1926, **6**, 156) comments on 65 cases in which the dye was administered in salol-coated capsules. In all of the cases with achlorhydria the shadow of the gall bladder was absent or faint, and there was little or no evidence of undissolved dye. Often in cases with high free HCl the shadow of the gall bladder was faint, and there was Roentgen ray evidence of lack of solution of the dye. He considers it probable that absorption is reduced in proportion to the free HCl in the stomach. However,

more dense shadows of the gall bladder were obtained in cases with normal gastric acidity than in cases with diminished or absent acidity. The author concludes that the alimentary reaction should be taken into account in interpreting cholecystograms, and that only a definite gall-bladder shadow has clinical value, the absence of a shadow being inconclusive.

Oral Administration of Sodium Tetraiodophenolphthalein.—BRAMS, MEYER and BRAMS (*Radiology*, 1926, **6**, 1) report the results of 100 cases. The dye was given in pills coated with stearic acid. In 40 cases the patients felt nauseated and a few vomited. Forty-three cases of this series were proven at operation to correspond with the roentgenologic diagnosis, and in 55 the clinical diagnosis was corroborated. The diagnosis was wrong in 2 surgically proved cases.

Sarcoma Complicating Osteitis Deformans.—Two cases are reported by CAMP (*Radiology*, 1925, **5**, 495). DaCosta found coincidence of malignant disease in 9.5 per cent of 213 collected cases of Paget's disease. Camp's first case was a man, aged seventy years, with sarcoma of the femur, and, in addition, a coarse trabeculation characteristic of Paget's disease. The second case was in a man, aged sixty years, who had a sarcoma of the left humerus, metastasis to the lungs, and Paget's disease of the right innominate and right tibia.

Evaluation of Treatment of Carcinoma of the Cervix with Radium.—Radium today is the best single therapeutic agent for the control of uterine cancer in the opinion of HEALY (*Am. J. Roentgenol. and Rad. Ther.*, 1925, **14**, 542), and its usefulness is not restricted to any one group of cases, but is indicated in every case which is not hopelessly advanced or complicated by extensive pelvic infection. His tabulated statistics show a high percentage of clinical cures, even after several years. He concludes that operation is justifiable only when serious contraindications to radium therapy are present.

Cholecystography and Operative Results in 182 Cases.—SARALEGUI (*Am. J. Roentgenol. and Rad. Ther.*, 1925, **14**, 514) describes his experience with both the bromin and iodin salt, given intravenously. The diagnostic results were good. On giving pituitrin contractions of the gall bladder were seen. In one instance an excellent shadow picture of the common duct, without any shadow of the gall bladder, was obtained. This suggested obstruction and dilatation of the common duct, both of which conditions were confirmed at operation.

Radiotherapy in Inoperable Carcinoma of the Cervix.—BROOKS (*Am. J. Roentgenol. and Rad. Ther.*, 1925, **14**, 541) classes as inoperable those cases having one or more of the following symptoms: (*a*) Severe sacral pain; (*b*) extension of the cancer from cervical vaginal mucosa to the vaginal mucosa; (*c*) fixation of the uterus in the cul de sac; (*d*) involvement of the rectum; (*e*) marked cachexia; (*f*) known metastasis. One hundred such cases had application of radium followed by deep Roentgen ray treatment. Eighteen patients are clinically well after one year, 11 after two years and 3 after three years.

NEUROLOGY AND PSYCHIATRY

UNDER THE CHARGE OF

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Brain Tumors in Children—Their General Symptomatology.—CRITCHLEY (*Brit. J. Child. Dis.*, 1925, **22**,) makes an analysis of 125 cases of brain tumors in children admitted to the Queen Square National Hospital, from 1912 to 1925. One case occurred during infancy and only 3 in the first thirty-six months of life. After this age the frequency gradually increases up to the age of eight years, after which time a fairly uniform level is maintained, varying from 9 to 14 cases at each age period up to sixteen years. The site of the tumors was as follows: 59, or 47.2 per cent, were situated in the pons or cerebellar peduncles; 34, or 27.2 per cent, were tumors of the cerebellum (14 were classed as pituitary or suprapituitary). Tuberculomata, usually multiple, were the most frequent type of tumor, followed by gliomata, sarcomata, gummata, endotheliomata and neurofibromata. Neurofibromata involved especially the olfactory and acoustic nerves. In discussing general symptomatology, the author stresses the importance of diagnosis before the development of the triad of headache, vomiting and papilledema. Headache is the most constant feature, but varies greatly in severity, character and position. Pain is less severe in children than in adults. Pituitary growths show pain referred to the temples—cerebellar tumors, as a rule, cause pain in the frontal region as well as in the nape of the neck. Headaches are usually worse in the early morning. Gradual change in the child's disposition may be the earliest symptom, and as intracranial pressure increases lethargy becomes marked. As a rule, psychomotor excitement, restlessness and delirium are not seen. Somnolence is a persistent feature from the onset in growths in the diencephalon and mesencephalon (as in encephalitis). Lesions around the aqueduct of Sylvius produce lethargy. Vomiting occurs in most patients, and in subtentorial growths is apt to precede the headache. In slow growing tumors endotheliomata it may be absent. This symptom is in proportion to the amount of pressure and corresponds to the degree of papilledema. Paralysis of various cranial nerves may result from increased intracranial pressure; thus the olfactory nerves may be pulled upon in cases of cerebellar tumor and produce anosmia; paralysis of the sixth nerve may occur with tumor in almost any part of the brain. The cranial sutures may separate and permit of transudation of fluid into the soft tissues of the scalp. A generalized thinning of the skull bones may occur and a peculiar flocculent appearance in the vault may be noted in skiagraphs. Percussion may produce a boxy note as described by MacEwen. As intracranial pressure increases the

reflexes may be abolished, the pupils dilate and react sluggishly and the pulse rate falls. Papilledema occurs in 80 per cent of the cases and appears earliest in subtentorial growths. If a decompression is not performed optic atrophy develops with more rapidity in children than in adults. Papilledema may occur in only one eye, the other eye being atrophic in frontal tumors. Convulsive attacks with and without consciousness may occur at any stage. These may be focal, Jacksonian, as in tumors in the motor cortex, or they may be generalized. Convulsions are uncommon in pontine and mesencephalic growths. In subtentorial tumors convulsive seizures consist of tonic rigidity, usually with no clonic stage and with the retention of consciousness throughout. Convulsive seizures often occur as the result of increased intracranial pressure alone. The physical development of the child is delayed and patients who survive, as a rule, are dwarfed, and often sexually and mentally infantile. In girls who have reached puberty the menses cease and the breasts fail to develop. In most instances the disease progresses rapidly. Remissions, however, occur and are characteristic of tumors occurring in childhood, especially of tuberculomata situated within the pontocerebellar regions.

On Atypical and Masked Forms of Encephalitis Epidemica (Lethargica) on a Basis of about 125 Cases.—NEEL (*J. Nerv. and Ment. Dis.*, 1926, **63**, 1) discusses a number of cases in Denmark, occurring between 1916 and 1922, that had been variously diagnosed, except epidemic encephalitis, but most of whom in reality he now feels had a mild or atypical form of epidemic encephalitis. Six of these occurred in 1916, and some before the announcement of the epidemics in Australia, France, Vienna and England. The spinal fluid showed a variation from a slight to a considerable increase in the cells, globulin and albumin. The symptoms shown in many of the cases, but not all of them, were fever, lethargy, insomnia, eye symptoms, speech disturbances, Babinski sign, hemiplegia, acute and chronic psychic disturbances, character, pain, myoclonic jerks, formication in hands, hiccoughing, optic neuritis. In 70 of 127 cases not previously diagnosed epidemic encephalitis he was able to prove that diagnosis subsequently. Some brains were examined microscopically, and these for the most part showed lesions characteristic of encephalitis. Such abortive forms tended to decline with the decline of the epidemic.

A Peculiar Reflex Phenomenon.—PALTHE (*Brain*, 1925, **48**, 476) describes a reflex which has often been observed by people when a strong current of cold air strikes one in the face. In such instances there is a "feeling of suffocation and a gasping for breath accompanied by a curious sensation in the throat." By experimental methods the author was able to demonstrate that to produce the reflex the stimulus must be cold and thrown against the proper zone with some force. Ether spray or a strong current of air were found very suitable. The only zone which will bring out the reflex is the upper lip. Occasionally a small zone below the lower lip will also produce it, and the most effectual area is the groove under the nostrils and the lower skin covered portion of the nasal septum. The reflex itself consists of an arrest of breathing in any phase, movement of floor of mouth and root

of tongue, increase of pressure in nasal cavities and movement of the larynx. It resembles much the swallowing reflex. The afferent path of the reflex is probably formed by the second branch of the trigeminal nerve, its ganglion and the root of the trigeminal nerve. The author presents cases to illustrate the localizing valve of this test. He thinks the reflex is a protective phenomenon much like the winking reflex.

PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF

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Splenomegaly (Type Gaucher) and Lipoid Histiocytosis (Type Niemann).—Since the description by Gaucher, in 1882, of an unusual symptom complex associated with large-cell splenomegaly, it would seem that we cannot separate from this group one to which Niemann has suggested the name "large-cell metamorphosis of glands." BLOOM (*Am. J. Path.*, 1925, **1**, 595) has made a study of these two types, and reports 2 cases of Gaucher's disease and 3 cases of (so-called) Niemann's disease. He finds a widespread infiltration of lipoid material in the reticulum cells of the spleen, lymph nodes, thymus, Kupffer cells, also in the large pale cells found in the alveoli and perivascular tissues of the lung. In sharp contrast, however, to the Gaucher cells, these will stain positively for the more complex lipoids. Moreover, they do not contain iron and are markedly vacuolated after treatment with absolute alcohol. In true Gaucher's disease he finds large pale cells which contain iron. These large cells have a marked longitudinal striation with Mallory's aniline-blue, connective-tissue staining method. The author suggests the name "lipoid histiocytosis" as a name for this condition, first described by Niemann, to convey the idea of a process involving the storage of lipoid material in the histocytes throughout the body.

Relation of Pregnancy to Carcinoma of Uterus.—Out of 500 cases of cancer of the uterus the cervix was involved in 406, 89.8 per cent occurred after the age of thirty-five, with the maximum incidence between 35 and 44. O'BRIEN (*J. Cancer Res.*, 1925, **9**, 391) submits the following figures with reference to the proportion of women in the cancer age who have borne children. From the 1920 census it was determined that only 9.71 per cent of women over thirty-five were unmarried. Another statistical study showed that of the women in the second decade of married life only 7.4 per cent had never been pregnant. These figures, while not indicating a direct dependence of cancer of the cervix on pregnancy, yet they do show that among those who have reached the cancer age parous women greatly dominate.

Autoplastic Implantation of Tar Tumors as Compared to their Histologic Picture.—KREYBERG (*J. Cancer Res.*, 1925, **9**, 381) finds a complete parallelism between the growth of autoplasts of tar tumors and their histological structure. No autoplastic inoculation of a histologically innocent tumor grew. Of those that were diagnosed as malignant some were prevented from growing by infection.

Sarcoma of the Heart in a Guinea-pig.—BENDER (*J. Cancer Res.*, 1925, **9**, 384) reports a sarcoma of the heart in a guinea-pig. This tumor was of the lymphoblastic type, and she believes it to be the only case reported.

Experimental Production of Gliosis.—A multiplication of glia cells (gliosis) is one of the common reactions of the nervous system to lesions. The exact cause, be it a purely mechanical replacement of the lost tissue or be it the toxins which injure and destroy the parenchymatous tissue that acts as a stimulus to the production of the less specialized supportive tissue or whether it is the products of degenerating nerve tissue that acts as the specific stimulus to glia cells, we do not know. BENSON (*Am. J. Path.*, 1925, **1**, 657), however, with the latter idea in mind, has completed a series of experiments. Using pure cholesterol intravenously in rabbits, she finds no effects on the nerve cells except possibly an increase in the lipoid content of the phagocytic cells of the meninges or perivascular spaces. Using it intraspinally caused a slight thickening of the dura, a marked increase in the cells of the arachnoid space that are phagocytic for cholesterol, and a mild increase in the glia cells of the periphery of the cord. Further experiments, using cerebrin, cholesterol, phospholipin and residue, extracts from a dog's brain, injected through a trephine opening over the parietal bone of a dog, were carried out according to the method given. Gliosis was least marked in the control animal and the one receiving the residue. It was increased by the cerebrin and most marked with phospholipin and cholesterol extracts. The fact that purified cholesterol failed to give a gliosis in the spinal cord in rabbits, suggests a common substance in phospholipin and cholesterol extracts which is not present in purified material that acts as a glia stimulant. Fibrous reaction in the form of a capsule was beginning in the cholesterol experiment and practically complete in the residue experiment. This fibrous reaction was least in the phospholipin injection and showed more in the cerebrin experiment. Calcification was evident in the phospholipin experiment.

A Multinucleated Liver-cell Carcinoma.—ROWEN and MALLORY (*Am. J. Path.*, 1925, **1**, 677) report an interesting case of liver-cell carcinoma which contained many huge multinucleated tumor cells apparently arising from multiple mitosis. The authors found 7 other liver-cell carcinomata in going over 6506 consecutive postmortem examinations. None of these showed the multinucleated cells however. All were in males, except 1; 1 was thirty-two years of age and the rest between forty-five and seventy-eight years. In 6 of the 7 cases cirrhosis was well marked and of the pigment type (hemochromatosis) in 3 and combined with hyalin (so-called alcoholic type) in the other 3. It would seem that the pigment cirrhosis is the type most commonly complicated by liver-cell carcinoma.

HYGIENE AND PUBLIC HEALTH

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A Disease in Wild Rats with Gross Pathology Resembling Plague.—WAYSON (*Pub. Health Repts.*, 1925, **40**, 1975), in the examination of rats with the object of detecting plague infection, encountered a condition closely simulating plague in some respects. The postmortem findings most frequently met were subcutaneous injection, enlarged congested lymph nodes, pleural effusion, mottled or stippled liver and enlarged spleen with rounded edges. In guinea pigs inoculated from infected rats death occurred usually in from thirty-six to forty-eight hours (while plague usually requires four to six days to kill). These animals show necrosis at site of inoculation, gelatinous edema, swollen lymph nodes, cloudy pleural and peritoneal exudates and congestion of intestines often with hemorrhages in the walls; the liver is grayish-red; spleen normal in size or slightly enlarged, often with fibrous exudate on the surface. Plague and the disease simulating it have been found coëxisting in the same rat. The causative organism is much smaller than the plague bacillus and is morphologically a coccobacillus or a bacillus. It is classed as a member of the hemorrhagic septicemia group.

The Administration of Mercurial Preparations in Leprosy—DENNEY, HOPKINS, WOOLEY and BARENTINE (*Pub. Health Repts.*, 1925, **40**, 1795) note that we are still without a specific for leprosy, though the impression is gaining that the disease is in some degree amenable to treatment. The earlier literature on mercury preparations is reviewed. The present report is based on the experience with 44 cases, nearly all of which have been under observation for a year or more. Patients were selected so as to cover the various stages of progress of the malady. The drug was given intravenously once each week in 1 per cent solution. The routine dose was 2.5 mg. per kilo of bodyweight. Double this dose was tried at the outset but was found to be excessive, as it gave rise to pronounced general reactions. The results were as follows: One patient absconded; 3 patients died during the period of treatment; 3 patients became considerably worse; 2 patients became slightly worse; 7 patients remained unchanged; 6 patients showed slight improvement; 6 patients showed moderate improvement; 16 patients showed marked improvement. The following comment and conclusions are given: "A very definite improvement was early apparent in some of the secondary lesions found in nodular and mixed types. Ulcerating nodules became clean, granulated and healed, leaving smooth

cicatrices. Trophic ulcers responded more slowly, but definitely improved. Occasionally soft nodules showed a very slow tendency to absorption; fibrous nodules were not noticeably improved. Symptoms referable solely to advanced anesthetic leprosy were not appreciably affected. Two cases of early maculoanesthetic leprosy were markedly improved as far as macules are concerned. It should be noted that in early maculoanesthetic leprosy macules often improve and even temporarily disappear without treatment. An interesting phenomenon occurred in approximately one-half of the patients who were accustomed to occasional unannounced attacks of leprous fever accompanied by outcroppings of evanescent tubercles. It was noted that sometimes after the first injection, and frequently after the second or third intravenous injection of mercurochrome, the course of the febrile reaction was apparently favorably modified by a sharp decline in the temperature within twelve hours and by the failure, or almost complete failure, of evanescent nodules to appear. In a few instances febrile reactions have not recurred. In many, however, after a period of two or three months' treatment leprous fever and evanescent tubercles reappeared, although they were rarely so severe as before treatment was started. Following the first few injections the majority of patients claimed a distinct improvement in general health and exhibited satisfactory improvement in certain leprous lesions and also in lesions due to secondary infections. This improvement continued for several months; subsequently, improvement was less rapid. Leprous patients in this experiment suffering from active pulmonary tuberculosis have not exhibited progressive improvement of both diseases; certain leprous manifestations have improved while the pulmonary tuberculosis has apparently been aggravated by mercurochrome. As a continuance of the study of mercurial preparations, and in addition to this experiment, which is being continued, a selected number of patients are being given further treatment by the intravenous administration of mercurophen and metaphen, a report of which will be made subsequently: (1) Mercurochrome soluble 220 has not not proved to be specific for leprosy. (2) Mercurochrome soluble 220 has been helpful in checking rapid retrogression in leprosy. (3) Mercurochrome soluble 220 has been of value in the treatment of ulcers, the result of disintegrating tubercles. (4) Mercurochrome soluble 220 has been helpful in the healing of neurotrophic ulcers. (5) Mercurochrome has not been helpful in checking the unfavorable progress of pulmonary tuberculosis in lepers; on the contrary, this complication was apparently aggravated."

Rocky Mountain Spotted Fever: Vaccination of Monkeys and Man.—SPENCER and PARKER (*Pub. Health Repts.*, 1925, **40**, 2159) used an emulsion of virulent infected ticks (Dermacentor andersonii) for the preparation of a vaccine which it is hoped may serve as a prophylactic. Experimentally in laboratory animals it was found to be effective in preventing the disease. In a single case it seemed to modify the course of the disease in a man who had been vaccinated very recently. The serum of vaccinated persons and of vaccinated animals was found to have acquired the ability to neutralize spotted-fever virus.

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Physical Properties of the Red Blood Cell.—W. SEIFRIZ (from the Department of Botany, University of Pennsylvania). Erythrocytes of the amphibian cryptobranchus (hell-bender) were subjected to microdissection, using the Péterfi (Zeiss) micromanipulator. A few observations were made on the human erythrocyte. The red blood cell of cryptobranchus is ellipsoidal, with a prominent central bulge occupied by the nucleus. It is, on an average, 46 μ long, 27 μ wide and 7 μ thick, the latter dimension tapering down to 2 μ at the edge. The corpuscle possesses a tough, highly elastic wall about 0.8 μ in thickness, which may be readily penetrated, torn or stretched by microneedles. The shape of the cell is determined by the rigidity of the wall. Normally quite rigid, it may become fluid enough to permit the formation of large globular protrusions, of papillæ and other abnormal processes, and this state of liquefaction may go so far as to apparently complete solubility of the wall in the saline medium. The corpuscle membrane is, therefore, not a purely static thing, but capable of change in its physical properties as is any living protoplasmic mass. The hemoglobin-containing contents of the red corpuscle is a very thin layer with maximum and minimum thickness of 2 and 0.5 μ. It is apparently a moderately viscous liquid, undoubtedly undergoing changes in consistency as does all protoplasm. When exposed by a tear in the cell wall the cytoplasm may retain its identity within the corpuscle, but this condition is not long maintained before disorganization brings on water miscibility of the cell contents and consequent loss of the cytoplasm. By tearing the corpuscle wall the large nucleus may be freed intact. When dissected it proves to be a soft jelly of extraordinary elastic properties. The nucleus when set free may remain and tolerate some minutes of dissection without evident change in its consistency. Ultimately, however, it coagulates, losing its elasticity and readily disintegrating. Observations on the human erythrocyte similar to those described above reveal identical properties, exclusive of the presence of a nucleus. The human red blood cell possesses a delicate but quite resistant pellicle which can be torn and stretched by microneedles. The hemoglobin appears to be a moderately viscous liquid.

Some Physicochemical Factors in the Formation of Gall Stones.—R. C. WEIMAR and J. E. SWEET (from the Department of Surgical Research, University of Pennsylvania School of Medicine). A study of the literature indicates that our ideas of the formation of gall stones are based upon two assumptions which appear so obvious that they have never been questioned. The first of these assumptions is that the radial arrangement of the crystals around a central mass must point

to a process of crystallization which starts at the center and progresses in all directions toward the periphery; the second assumption is that the common appearance in the cross section of the gall stone of what seem to be distinct layers points to a gradual growth by accretion. The first assumption was tested by filling a thin-walled glass ball with melted cholesterol and then quickly chilling the mass in order to start the crystallization on the periphery. Such an artificial "stone," broken in halves, shows a structure so like that of real gall stones that no one, pathologist or surgeon, has thus far been able to correctly sort a collection of gall stones and such artificial "stones." The second assumption was tested by studying the formation of Liesegang's rings in masses of dichromate gelatin which are similar in shape to the various types of gall stones, and which have been immersed in silver nitrate solution, or in such masses in the center of which had been placed a drop of silver nitrate. The results show very clearly that concentric rings appear in globular masses; that in triangular forms the apparent lamellations may be limited to the corners; while in cuboidal forms the precipitated silver dichromate may appear in greater amount in the angles. In other words, the apparent lamellation of gall stones can be reproduced in all its peculiarities by the Liesegang phenomenon as it appears in such geometric masses of gelatin. The possibility is suggested that gall stones do not of necessity arise as a gradual accretion and crystallization around a "nucleus;" but that they may begin as colloidal masses, which are molded into the shape in which we find them, and in which the apparent lamellation and the crystallization process then go forward to form hardened gall stones.

Perspiratio Insensibilis: Its Significance in Physiology and Pathology and its Relationship to Skin Temperature and Heat Loss.—F. G. BENEDICT (from the Carnegie Institution of Washington, Nutrition Laboratory, Boston).

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